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# Nickel: Ambient Water Quality Criteria

(U.S.) Environmental Protection Agency, Washington, DC

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# NICKEL

## Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

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# BIBLIOGRAPHIC INFORMATION

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for nickel. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi····

KEYWORDS: *Water quality, *Toxicology, *Nickel, *Toxic substances, *Water pollution effects(Humans).

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# CRITERION DOCUMENT

# NICKEL

## CRITERIA

### Aquatic Life

For nickel the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$ as a 24-hour average and the concentration should not exceed "$e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}$" at any time.

The data base for saltwater aquatic life is insufficient to allow use of the Guidelines. The following recommendation is inferred from toxicity data for freshwater organisms.

For nickel the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 220 µg/l as a 24-hour average and the concentration should not exceed 510 µg/l at any time.

### Human Health

For the protection of human health based on the toxic properties of nickel ingested through water and through contaminated aquatic organisms, the ambient water criterion is determined to be 133 µg/l/day.

## Introduction

Nickel is a bright, silver metal of the iron-cobalt-nickel triad. It is a hard and malleable metal with a high tensile strength and is used in electroplating and virtually all areas of metallurgy. It is a divalent metal, with characteristic divalent metal chemistry, although it does not readily form chloro-complexes and under environmental conditions would not be expected to form significant amounts of sulfate complexes. Nickel levels in U.S. drinking waters are typically less than 10 µg/l (Durfor and Becker, 1962).

In the aquatic environment nickel is acutely toxic to fishes at concentrations as low as 2,480 µg/l (Lind, et al. manuscript). Chronic toxicity to fishes has been reported at 433 µg/l (Lind, et al. manuscript). Water quality also affects nickel toxicity. For instance, Lind, et al. (manuscript) found the lowest effect level for fathead minnows to lie between 109 and 433 µg/l in embryo-larval tests in water with a hardness of 44 mg/l as calcium carbonate, while Pickering (1974) reported a range 380 to 730 µg/l in a life cycle test with the same species at a water hardness of 210 mg/l as calcium carbonate.

The human health criterion is calculated on the basis of adverse effects seen in rats provided with drinking water containing 5 ppm nickel. These effects included reduction of litter size, increased numbers of runts, and increased neonatal mortality (Schroeder and Mitchener, 1971).

## AQUATIC LIFE TOXICOLOGY*

## FRESHWATER ORGANISMS

### Introduction

Nickel is a common component of natural freshwaters and can occur at concentrations less than 1 µg/l in areas impacted to a minimal degree by man. As with other divalent heavy metals, free nickel ($Ni^{2+}$) may participate in various types of aqueous chemical reactions such as adsorption, precipitation, complexation, and bioaccumulation. Since the chemical environment of nickel is changed in these processes, its toxicity may also be changed.

Equilibrium calculations using various chemical components common to natural freshwaters reveal that very few known reactions with nickel would be expected to occur, to any great extent, with anions such as sulfate, chloride, and carbonate. For example, chloride is not an important complexing agent, since its concentration would have to be greater than that of typical salt water to form the nickel chloride complex. Sulfate concentrations

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

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would have to approach about $10^{-2}$M concentrations (an unlikely natural condition) before approximately one-half of the nickel would be complexed. Although precipitation by carbonate is possible, this reaction is also relatively unimportant since conditions conducive to its occurrence appear unlikely.

With respect to more reactive substances, complexation by organic complexing agents such as aminopolycarboxylic acids is possible. At present, equilibria with natural substances such as suspended clays, humic acids, and microorganisms is generally poorly understood. Therefore, as a first approximation, the most prevalent form of nickel in toxicity test systems with low concentrations of suspended solids and dissolved organic matter is estimated to be the free form, $Ni^{2+}$.

## Acute Toxicity

Adjusted LC50 values for fish (Table 1) ranged from 2,433 µg/l for the guppy (hardness = 20 mg/l) to 48,881 µg/l for the bluegill (hardness = 42 mg/l). At comparable hardness values (20-29 mg/l), several of the lowest adjusted LC50 values (5,368, 2,832, 2,504, 2,916, 2,923, 2,433, 2,480, 2,832, and 2,930 µg/l) generally appear to be relatively similar for five different species of fish: goldfish, fathead minnow, guppy, rock bass, and bluegill (Pickering and Henderson, 1966, and Lind et al., manuscript). At the high end of the hardness scale (360 mg/l), there are three adjusted LC50 values (23,180, 24,328, 21,649 mg/l) which also appear relatively close for two species of fish, fathead minnow and bluegill (Pickering and Henderson, 1966). However, in some cases, greater variability (15,800, 26,663, 23,898, 7,406 µg/l) was observed at comparable hardness levels (42 mg/l) for four different species of trout (Willford, 1966).

The toxicity data in Table 1 indicate that water hardness significantly influences the acute toxicity of nickel to fish.

Following the Guidelines, an exponential equation describing the relationship of toxicity to hardness for each species was fit by least squares regression of the natural logarithms of the toxicity values and hardness. For nickel, sufficient acute toxicity data and hardness ranges were available for two fish species to fit regression equations. The slope of these equations ranged from 0.86 for the fathead minnow to 0.63 for the bluegill, with a geometric mean of 0.74.

As a measure of relative species sensitivity to nickel, logarithmic intercepts were calculated for each species by fitting the mean slope (0.74) through the geometric mean toxicity value and hardness for each species. These intercepts varied from 5.41 for rock bass to 7.45 for banded killifish, with an arithmetic average of 6.28 for all 16 fish species. This variation in logarithmic intercepts indicates a range of species sensitivity to nickel of only seven fold. The Final Fish Acute Value is derived using the geometric mean slope (0.74), the adjusted average intercept (4.92), and the species sensitivity factor (3.9).

In comparison to the results for fish, acute tests with invertebrate species (Table 2) generally have a greater range of adjusted LC50 values at a fixed hardness. The caddisfly exhibited the highest adjusted value (33,220 µg/l, Rehwoldt et al., 1973) and Daphnia magna (Biesinger and Christensen, 1972) gave the lowest value (432 µg/l). Lind et al. (manuscript) provided the only data obtained under relatively high hardness conditions (244 mg/l).

Sufficient data were available for only one invertebrate species, Daphnia pulicaria, to demonstrate the relationship of toxicity to hardness, and the resulting slope is 0.47. As a measure of relative species sensitivity to nickel, logarithmic intercepts were calculated for each species by fitting the slope through the geometric mean toxicity value and hardness for each species. These intercepts ranged from 4.67 for Daphnia magna to 8.57 for the caddisfly with an arithmetic average of 7.23 for all 11 species.

The Final Invertebrate Acute Value is derived using the geometric mean slope (0.47), the adjusted average intercept (4.19) and the species sensitivity factor (21). Since this value is lower than the one for fish, this one becomes the Final Acute Value.

## Chronic Toxicity

A life cycle test (Pickering, 1974) and an embryo-larval test (Lind et al., manuscript) have been conducted with the fathead minnow (Table 3) and the chronic values are 527 µg/l, at a hardness of 210 mg/l, and 109 µg/l, at a hardness of 44 mg/l, respectively. These two chronic values for the fathead minnow give a slope of 1.01 and an intercept of 0.88. Use of the species sensitivity factor of 6.7 results in a Final Fish Chronic Value based on a slope of 1.01 and an intercept of -1.02.

Biesinger and Christensen (1972) conducted a life cycle test with Daphnia magna, which resulted in a chronic value of 53 µg/l (Table 4) at a hardness of 45 mg/l. Due to the lack of data for chronic toxicity to invertebrate species, the slope of 1.01 from the fish chronic data must be assumed. Since daphnids were the most sensitive invertebrate species to nickel in acute tests, it would appear to be inappropriate to use the species sensitivity factor of 5.1 with the chronic data. Thus the Final Invertebrate Chronic Value is derived using the slope of 1.01 and an intercept of 0.13. Since the Final Fish Chronic Value is lower, it becomes the Final Chronic Value.

## Plant Effects

Hutchinson (1973) and Hutchinson and Stokes (1975) observed reduced growth of several algal species at concentrations ranging from 100 to 700 µg/l (Table 5). The relationship between these results and the 24-hour average concentrations derived as the criterion is not known, since the hardness of the test waters used was not stated. Although a decrease in diatom diversity was observed by Patrick et al. (1975) to occur at concentrations as low as 2 µg/l (Table 7), the possible effects this may have are uncertain. The occurrence of slight changes in diversity due to nickel may or may not be significantly deleterous to ecological functions and biomass production. It should initiate further consideration and study since these changes occurred at concentrations below the criterion. Since the values in Table 5 are higher than the chronic data on fish and invertebrate species, plant effects are presently not used in determining the criterion.

## Residues

The only available bioconcentration factors (BCF) are for the fathead minnow (Lind et al., manuscript) and an alga (Hutchinson and Stokes, 1975). The BCF for the whole body of the fathead minnow was 61 and for the alga the BCF was 9.8 (Table 6). The geometric mean BCF is 24.

Since no maximum permissible tissue concentration is available, no Residue Limited Toxicant Concentration can be calculated.

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## CRITERION FORMULATION

### Freshwater-Aquatic Life

### Summary of Available Data

All concentrations herein are expressed in terms of nickel. The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = $e^{(0.74 \cdot \ln(\text{hardness}) + 4.92)}$

Final Invertebrate Acute Value = $e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}$

Final Acute Value = $e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}$

Final Fish Chronic Value = $e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$

Final Invertebrate Chronic Value = $e^{(1.01 \cdot \ln(\text{hardness}) + 0.13)}$

Final Plant Value = 100 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = $e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$

The maximum concentration of nickel is equal to the Final Acute Value as given by $e^{(0.47 \cdot \ln(\text{hardness} + 4.19)}$ and the 24-hour average concentration is the Final Chronic Value as given by $e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$. No important adverse effec on freshwater organisms have been reported to be caused by concentrations lower than the 24-hour average concentration other than the possible changes in diatom diversity discussed earlier.

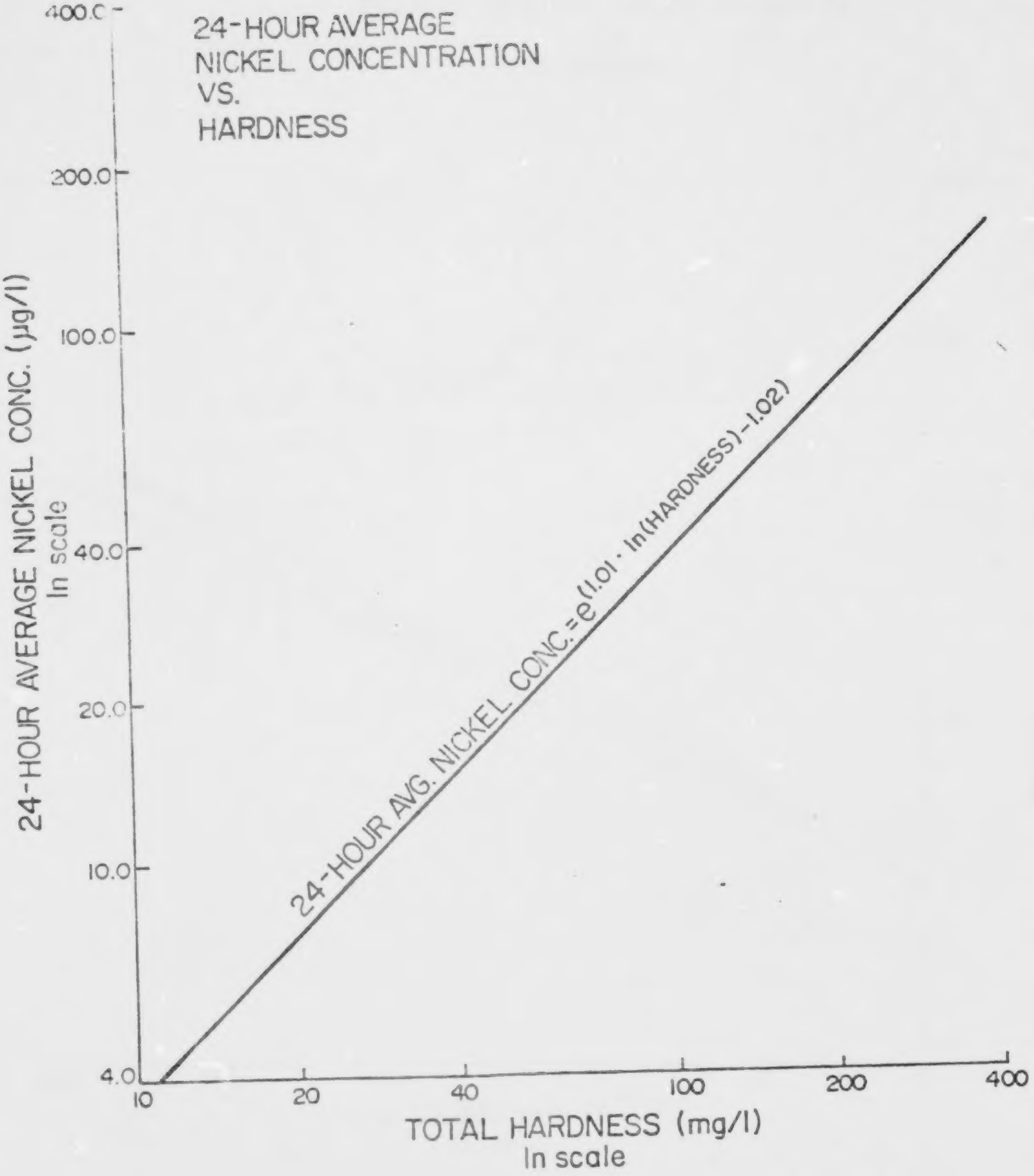
The final values can also be expressed as follows:

Final Fish Acute Value = 14,000 µg/l

Final Invertebrate Acute Value = 510 µg/l

Final Acute Value = 510 µg/l

CRITERION: For nickel, the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$" as a 24-hour average and the concentration should not exceed "$e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}$" at any time.


24-HOUR AVERAGE
NICKEL CONCENTRATION
VS.
HARDNESS
24-HOUR AVERAGE NICKEL CONC. (µg/l)
ln scale
400.0
200.0
100.0
40.0
20.0
10.0
4.0
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale
24-HOUR AVG. NICKEL CONC.=$e^{(1.01 \cdot \ln(\text{HARDNESS})-1.02)}$

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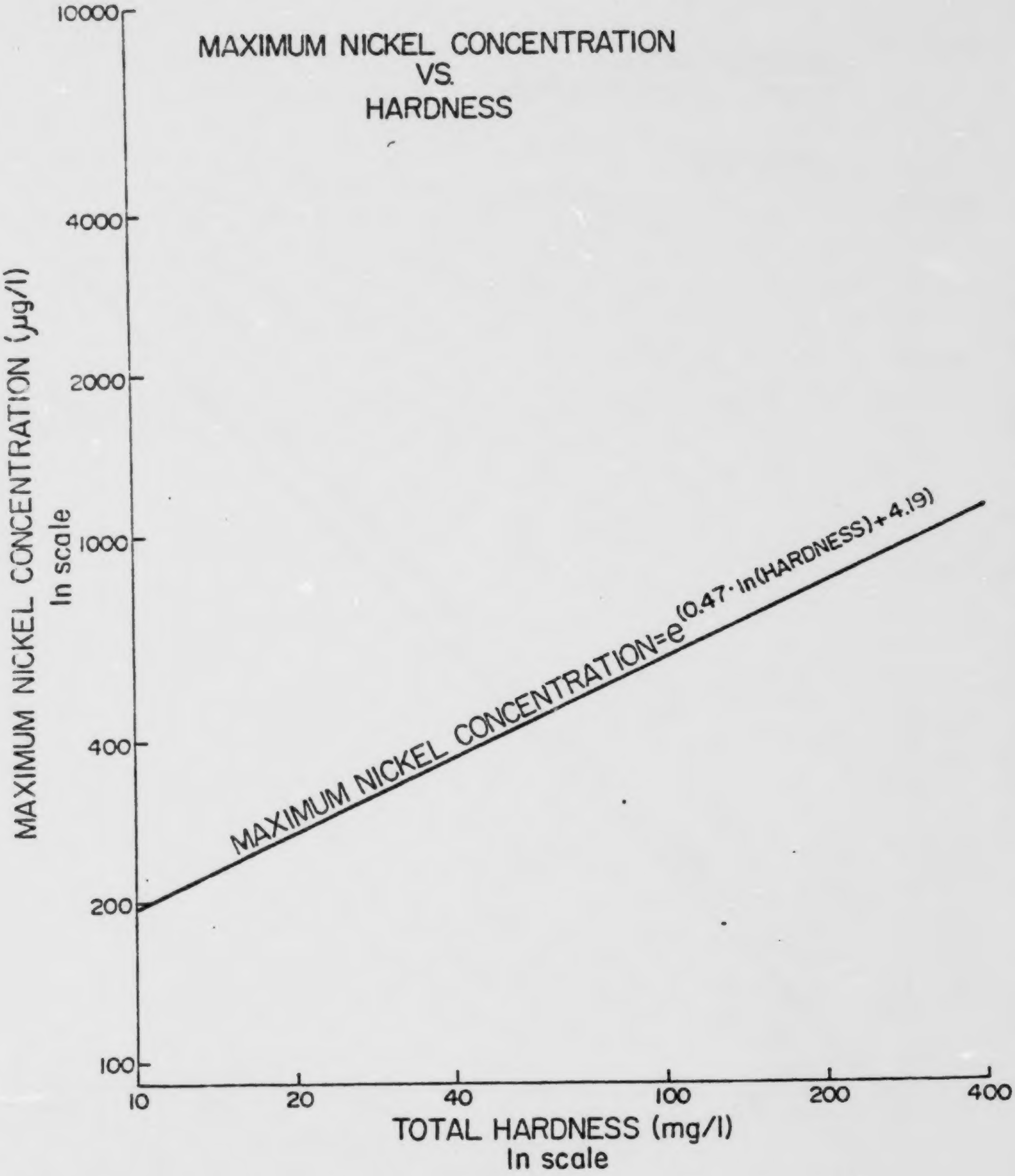
MAXIMUM NICKEL CONCENTRATION
VS.
HARDNESS
10000
4000
2000
1000
400
200
100
MAXIMUM NICKEL CONCENTRATION (µg/l)
ln scale
MAXIMUM NICKEL CONCENTRATION=e(0.47·ln(HARDNESS)+4.19)
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

Table 1. Freshwater fish acute values for nickel

| Organism | Bioassay Method* | Test Conc.** | Hardness (mg/l as $CaCO_3$) | Time (hrs) | LC50 (µg/l) | Adjusted LC50 (µg/l) | Reference |
|---|---|---|---|---|---|---|---|
| American eel, *Anguilla rostrata* | S | M | 53 | 96 | 13,000 | 9,230 | Rehwoldt, et al. 1971 |
| American eel, *Anguilla rostrata* | S | M | 55 | 96 | 13,000 | 9,230 | Rehwoldt, et al. 1972 |
| Rainbow trout, *Salmo gairdneri* | FT | M | -- | 96 | 35,500 | 35,500 | Hale, 1977 |
| Rainbow trout, *Salmo gairdneri* | R | U | 240 | 48 | 32,000 | 14,170 | Brown & Dalton, 1970 |
| Rainbow trout, *Salmo gairdneri* | S | U | 42 | 48 | 35,680 | 15,800 | Willford, 1966 |
| Brown trout, *Salmo trutta* | S | U | 42 | 48 | 60,210 | 26,663 | Willford, 1966 |
| Brook trout, *Salvelinus fontinalis* | S | U | 42 | 48 | 53,966 | 23,898 | Willford, 1966 |
| Lake trout, *Salvelinus namaycush* | S | U | 42 | 48 | 16,725 | 7,406 | Willford, 1966 |
| Goldfish, *Carassius auratus* | S | U | 20 | 96 | 9,820 | 5,368 | Pickering & Henderson, 1966 |
| Fathead minnow, *Pimephales promelas* | S | U | 210 | 96 | 27,000 | 14,761 | Pickering, 1974 |
| Fathead minnow, *Pimephales promelas* | S | M | 210 | 96 | 32,200 | 22,862 | Pickering, 1974 |
| Fathead minnow, *Pimephales promelas* | FT | M | 210 | 96 | 28,000 | 28,000 | Pickering, 1974 |
| Fathead minnow, *Pimephales promelas* | FT | M | 210 | 96 | 25,000 | 25,000 | Pickering, 1974 |
| Fathead minnow, *Pimephales promelas* | S | U | 20 | 96 | 5,180 | 2,832 | Pickering & Henderson, 1966 |
| Fathead minnow, *Pimephales promelas* | S | U | 20 | 96 | 4,580 | 2,504 | Pickering & Henderson, 1966 |

Table 1. (Continued)

| Organism | Bioassay Method* | Test Conc.** | Hardness (mg/l as CaCO$_3$) | Time (hrs) | LC50 (ug/l) | Adjusted LC50 (ug/l) | Reference |
|---|---|---|---|---|---|---|---|
| Fathead minnow, *Pimephales promelas* | S | U | 360 | 96 | 42,400 | 23,180 | Pickering & Henderson, 1966 |
| Fathead minnow, *Pimephales promelas* | S | U | 360 | 96 | 44,500 | 24,328 | Pickering & Henderson, 1966 |
| Fathead minnow, *Pimephales promelas* | FT | M | 45 | 96 | 5,209 | 5,209 | Lind, et al., Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 44 | 96 | 5,163 | 5,163 | Lind, et al. Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 29 | 96 | 2,916 | 2,916 | Lind, et al. Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 28 | 96 | 2,923 | 2,923 | Lind, et al., Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 77 | 96 | 12,356 | 12,356 | Lind, et al. Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 89 | 96 | 17,678 | 17,678 | Lind, et al. Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 91 | 96 | 8,617 | 8,617 | Lind, et al. Manuscript |
| Fathead minnow, *Pimephales promelas* | FT | M | 86 | 96 | 5,383 | 5,383 | Lind, et al. Manuscript |
| Carp, *Cyprinus carpio* | S | M | 53 | 96 | 10,600 | 7,526 | Rehwoldt, et al. 1971 |
| Carp, *Cyprinus carpio* | S | M | 55 | 96 | 10,400 | 7,384 | Rehwoldt, et al. 1971 |
| Channel catfish, *Ictalurus punctatus* | S | U | 42 | 48 | 36,795 | 16,294 | Willford, 1966 |
| Banded killifish, *Fundulus diaphanus* | S | M | 53 | 96 | 46,200 | 32,802 | Rehwoldt, et al. 1971 |
| Banded killifish, *Fundulus diaphanus* | S | M | 55 | 96 | 46,100 | 32,731 | Rehwoldt, et al. 1972 |
| Guppy, *Lebistes reticulatus* | S | U | 20 | 96 | 4,450 | 2,433 | Pickering & Henderson, 1966 |

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Table 1. (Continued)

| Organism | Bioassay Method * | Test Conc. ** | Hardness (mg/l as $CaCO_3$) | Time (hrs) | LC50 (ug/l) | Adjusted LC50 (ug/l) | Reference |
|---|---|---|---|---|---|---|---|
| Rock bass, Ambloplites rupestris | FT | M | 26 | 96 | 2,480 | 2,480 | Lind, et al. Manuscript |
| Striped bass, Roccus saxatilus | S | M | 53 | 96 | 6,200 | 4,402 | Rehwoldt, et al. 1971 |
| Striped bass, Roccus saxatilus | S | M | 55 | 96 | 6,300 | 4,473 | Rehwoldt, et al. 1972 |
| Pumpkinseed, Lepomis gibbosus | S | M | 53 | 96 | 8,100 | 5,751 | Rehwoldt, et al. 1971 |
| Pumpkinseed, Lepomis gibbosus | S | M | 55 | 96 | 8,000 | 5,680 | Rehwoldt, et al. 1972 |
| Bluegill, Lepomis macrochirus | S | U | 20 | 96 | 5,180 | 2,832 | Pickering & Henderson, 1966 |
| Bluegill, Lepomis macrochirus | S | U | 20 | 96 | 5,360 | 2,930 | Pickering & Henderson, 1966 |
| Bluegill, Lepomis macrochirus | S | U | 360 | 96 | 39,600 | 21,649 | Pickering & Henderson, 1966 |
| Bluegill, Lepomis macrochirus | S | U | 42 | 48 | 110,385 | 48,881 | Willford, 1966 |
| White perch, Roccus americanus | S | M | 53 | 96 | 13,600 | 9,656 | Rehwoldt, et al. 1971 |
| White perch, Roccus americanus | S | M | 55 | 96 | 13,700 | 9,727 | Rehwoldt, et al. 1972 |

* S = static, FT = flow-through

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

Fathead minnow: slope = 0.86, intercept = 5.30, r = 0.94, p = 0.01, N = 16

Bluegill: slope = 0.63, intercept = 6.72, r = 0.60, Not significant, N = 4

Geometric mean slope = 0.74

Average intercept for 16 fish species = 6.28

Adjusted average intercept = 6.28-ln(3.9) = 4.92

Final Fish Acute Value = $e^{(0.74 \cdot \ln(\text{hardness}) + 4.92)}$

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Table 2. Freshwater invertebrate acute values for nickel

| Organism | Bioassay Method* | Test Conc.** | Hardness (mg/l as $CaCO_3$) | Time (hrs) | LC50 (ug/l) | Adjusted LC50 (ug/l) | Reference |
|---|---|---|---|---|---|---|---|
| Rotifer, *Philodina acuticornus* | R | U | 25 | 96 | 2,900 | 2,456 | Buikema, et al. 1974 |
| Rotifer, *Philodina acuticornus* | R | U | 25 | 96 | 7,400 | 6,268 | Buikema, et al. 1974 |
| Bristleworm, *Nais* sp. | S | M | 50 | 96 | 14,100 | 15,510 | Rehwoldt, et al. 1973 |
| Snail (egg), *Amnicola* sp. | S | U | 50 | 96 | 11,400 | 12,540 | Rehwoldt, et al. 1973 |
| Snail (adult), *Amnicola* sp. | S | U | 50 | 96 | 14,300 | 15,730 | Rehwoldt, et al. 1973 |
| Cladoceran, *Daphnia hyalina* | S | U | -- | 48 | 1,900 | 1,609 | Baudouin & Scoppa, 1974 |
| Cladoceran, *Daphnia magna* | S | U | 45 | 48 | 1,120 | 949 | Biesinger & Christensen, 1972 |
| Cladoceran, *Daphnia magna* | S | U | 45 | 48 | 510 | 432 | Biesinger & Christensen, 1972 |
| Cladoceran, *Daphnia pulicaria* | R | M | 48 | 48 | 2,182 | 2,400 | Lind, et al. Manuscript |
| Cladoceran, *Daphnia pulicaria* | R | M | 48 | 48 | 1,813 | 1,994 | Lind, et al. Manuscript |
| Cladoceran, *Daphnia pulicaria* | R | M | 44 | 48 | 1,836 | 2,020 | Lind, et al. Manuscript |
| Cladoceran, *Daphnia pulicaria* | R | M | 29 | 48 | 697 | 767 | Lind, et al. Manuscript |
| Cladoceran, *Daphnia pulicaria* | R | M | 28 | 48 | 1,140 | 1,254 | Lind, et al. Manuscript |
| Cladoceran, *Daphnia pulicaria* | R | M | 28 | 48 | 1,034 | 1,137 | Lind, et al. Manuscript |
| Cladoceran, *Daphnia pulicaria* | R | M | 86 | 48 | 3,316 | 3,648 | Lind, et al. Manuscript |

Table 2. (Continued)

| Organism | Bioassay Method* | Test Conc.** | Hardness (mg/l as $CaCO_3$) | Time (hrs) | LC50 (ug/l) | Adjusted LC50 (ug/l) | Reference |
|---|---|---|---|---|---|---|---|
| Cladoceran, Daphnia pulicaria | R | M | 44 | 48 | 1,901 | 2,091 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 94 | 48 | 3,162 | 3,478 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 144 | 48 | 3,826 | 4,209 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 244 | 48 | 3,304 | 3,634 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 94 | 48 | 2,470 | 2,717 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 144 | 48 | 2,470 | 2,717 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 244 | 48 | 2,409 | 2,650 | Lind, et al. Manuscript |
| Clacoderan, Daphnia pulicaria | R | M | 84 | 48 | 3,014 | 3,315 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 74 | 48 | 2,325 | 2,558 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 73 | 48 | 3,414 | 3,755 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 100 | 48 | 3,757 | 4,133 | Lind, et al. Manuscript |
| Cladoceran, Daphnia pulicaria | R | M | 25 | 48 | 2,171 | 2,388 | Lind, et al. Manuscript |
| Copepod, Cyclops abyssorum | S | U | -- | 48 | 15,000 | 12,705 | Baudouin & Scoppa, 1976 |
| Copepod, Eudiaptomus padanus | S | U | -- | 48 | 3,600 | 3,049 | Baudouin & Scoppa, 1976 |
| Scud, Gammarus sp. | S | M | 50 | 96 | 13,000 | 14,300 | Rehwoldt, et al. 1973 |

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Table 2. (Continued)

| Organism | Bioassay Method* | Test Conc.** | Hardness (mg/l as $CaCO_3$) | Time (hrs) | LC50 (µg/l) | Adjusted LC50 (µg/l) | Reference |
|---|---|---|---|---|---|---|---|
| Mayfly, *Ephemerella subvaria* | S | U | 42 | 96 | 4,000 | 3,388 | Warnick & Bell, 1969 |
| Stonefly, *Acroneuria lycorias* | S | U | 40 | 96 | 33,500 | 28,374 | Warnick & Bell, 1969 |
| Damselfly, (unidentified) | S | M | 50 | 96 | 21,200 | 23,320 | Rehwoldt, et al. 1973 |
| Midge, *Chironomus* sp. | S | M | 50 | 96 | 8,600 | 9,460 | Rehwoldt, et al. 1973 |
| Caddisfly, (unidentified) | S | M | 50 | 96 | 30,200 | 33,220 | Rehwoldt, et al. 1973 |

* S = static, R = renewal

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

*Daphnia pulicaria*: slope = 0.47, intercept = 5.80, r = 0.72, p = 0.01, N = 19

Geometric mean slope = 0.47 (only value available)

Average intercept for 11 invertebrate species = 7.23

Adjusted average intercept = 7.23-ln(21) = 4.19

Final Invertebrate Acute Value = $e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}$

Table 3. Freshwater fish chronic values for nickel

| Organism | Test* | Limits (ug/l) | Chronic Value (ug/l) | Hardness (mg/l as $CaCO_3$) | Reference |
|---|---|---|---|---|---|
| Fathead minnow, _Pimephales promelas_ | LC | 380-730 | 527 | 210 | Pickering, 1974 |
| Fathead minnow, _Pimephales promelas_ | E-L | 109-433 | 109 | 44 | Lind, et al. Manuscript |

* LC = life cycle or partial life cycle, E-L = embryo-larval

Adjusted chronic values vs. hardness:

Fathead minnow: slope = 0.01, intercept = 0.88, Not significant, N = 2

Geometric mean slope = 1.01 (only value available)

Average intercept = 0.88 (only value available)

Adjusted average intercept = 0.88-ln(6.7) = -1.02

Final Fish Chronic Value = $e^{(1.01 \cdot \ln(\text{hardness})-1.02)}$

**Application Factor Values**

| Species | 96-hr LC50 (µg/l) | MATC (µg/l) | AF | Reference |
|---|---|---|---|---|
| Fathead minnow, _Pimephales promelas_ | 26,458 | 527 | 0.020 | Pickering, 1974 |

Table 4. Freshwater invertebrate chronic values for nickel (Biesinger & Christensen, 1972)

| Organism | Test * | Limits (ug/l) | Chronic Value (ug/l) | Hardness (mg/l as $CaCO_3$) |
|---|---|---|---|---|
| Cladoceran, *Daphnia magna* | LC | 30-95 | 53 | 45 |

* LC = life cycle or partial life cycle

Adjusted chronic values vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Using the slope (1.01) from the fish chronic values, the intercept for *D. magna* = 0.13 (only species tested).

Final Invertebrate Chronic Value = $e^{(1.01 \cdot \ln(\text{hardness}) + 0.13)}$

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Table 5. Freshwater plant effects for nickel

| Organism | Effect | Concentration (ug/l) | Reference |
|---|---|---|---|
| Alga, *Chlamydomonas eugametos* | Reduced growth | 700 | Hutchinson, 1973 |
| Alga, *Chlorella vulgaris* | Reduced growth | 500 | Hutchinson, 1973 |
| Alga, *Haematococcus capensis* | Reduced growth | 300 | Hutchinson, 1973 |
| Alga, *Scenedesmus acuminata* | Reduced growth | 500 | Hutchinson & Stokes, 1975 |
| Alga, *Scenedesmus acuminata* | Reduced growth | 100 | Hutchinson, 1973 |

Lowest plant value = 100 µg/l

**Table 6.** Freshwater residues for nickel

| Organism | Bioconcentration Factor | Time (days) | Reference |
|---|---|---|---|
| Alga,<br>Scenedesmus acuminata | 9.8 | 6 | Hutchinson & Stokes, 1975 |
| Fathead minnow,<br>Pimephales promelas | 61 | 30 | Lind, et al. Manuscript |

Geometric mean bioconcentration factor for all species = 24

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Table 7. Other freshwater data for nickel

| Organism | Test Duration | Effect | Hardness (mg/l as $CaCO_3$) | Result (ug/l) | Reference |
|---|---|---|---|---|---|
| Algae, (mixed population) | ≤53 days | Decrease in diatom diversity; population shift to blue and blue-green algae | 87 to 99 | 2 to 8.6 | Patrick, et al. 1975 |
| Cladoceran, Daphnia magna | 64 hrs | Immobilization | -- | <317 | Anderson, 1948 |

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## SALTWATER ORGANISMS

### Introduction

The scientific literature on nickel toxicity to saltwater organisms is limited. There are no chronic or residue data with fish or invertebrate species. The fish acute and plant data represent two species. This limited data base indicates that nickel is less toxic than such metals as mercury, copper, silver, and cadmium, and more toxic than chromium, manganese and aluminum.

### Acute Toxicity

Data on the acute toxicity of nickel to saltwater fishes is limited (Table 8). The adjusted values range from 14,586 µg/l for the Atlantic silverside to 191,345 µg/l for the mummichog. A third fish species, winter flounder (Table 11), has a 96-hour LC50 greater than 33,000 µg/l. The geometric mean of the fish acute data is 52,830 µg/l which when divided by the species sensitivity factor of 3.7 results in a Final Fish Acute Value of 14,000 µg/l.

The invertebrate acute toxicity data base consists of 14 data with a range of adjusted values from 262 µg/l for larvae of the hard clam (Calabrese and Nelson, 1974) to 271,040 µg/l for adults of the soft-shell clam (Eisler and Hennekey, 1977). The geometric mean of the invertebrate data is 24,970 µg/l which when adjusted for species sensitivity gives a Final Invertebrate Acute Value of 510 µg/l. This value appears to be protective of 95 percent of the species since only one data point is less than 510 µg/l. Most of the data on adults of macroinvertebrate species, the larval molluscan data and the planktonic copepod data indicate a need to test more sensitive species and life history stages.

Since the Final Invertebrate Acute Value of 510 μg/l is less than the Final Fish Acute Value, 14,000 μg/l, the Final Acute Value is 510 μg/l.

## Plant Effects

There was a 50 percent inactivation of photosynthesis of the giant kelp (Clendenning and North, 1959) at a nickel concentration of 2,000 μg/l (Table 10). Skaar et al. (1974) observed reduced growth of the alga, *Phaeodactylum tricornutum*, at a concentration of 1,000 μg/l (Table 10).

## Miscellaneous

These data indicate that embryos of the sea urchin are sensitive to nickel (Timourian and Watchmaker, 1972). Delayed development occurred at 58 μg/l but abnormal effects were noted at 580 μg/l after only twenty hours exposure. At this time, the delayed development observed at 58 μg/l does not appear to be important enough to be the basis for the 24-hour average concentration criterion.

## CRITERION FORMULATION

### Saltwater-Aquatic Life

### Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of nickel.

Final Fish Acute Value = 14,000 µg/l
Final Invertebrate Acute Value = 510 µg/l
Final Acute Value = 510 µg/l
Final Fish Chronic Value = not available
Final Invertebrate Chronic Value = not available
Final Plant Value = 1,000 µg/l
Residue Limited Toxicant Concentration = not available
Final Chronic Value = 1,000 µg/l
0.44 x Final Acute Value = 220 µg/l

No saltwater criterion can be derived for nickel using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures. Results obtained with nickel and freshwater fish indicate how a criterion may be derived.

An application factor of 0.020 was obtained for nickel with fathead minnows. Multiplying this value times the Final Acute Value for saltwater fish results in an estimated Final Chronic Value for saltwater fish of 0.020 x 14,000 µg/l = 280 µg/l, which is higher than 0.44 times the Final Acute Value for saltwater organisms.

The maximum concentration is the Final Acute Value of 510 µg/l and the 24-hour average concentration if 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For nickel the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 220 µg/l as a 24-hour average and the concentration should not exceed 510 µg/l at any time.

Table 8. Marine fish acute values for nickel

| Organism | Bioassay Method * | Test Conc.** | Time (hrs) | LC50 (ug/l) | Adjusted LC50 (ug/l) | Reference |
|---|---|---|---|---|---|---|
| Mummichog, *Fundulus heteroclitus* | S | U | 96 | 350,000 | 191,345 | Eisler & Hennekey, 1977 |
| Atlantic silverside, *Menidia menidia* | S | U | 72 | 29,000 | 14,586 | U.S. EPA, 1973 |

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* S = Static

** U = unmeasured

Geometric mean of adjusted values = 52,830 μg/l    $\frac{52,830}{3.7}$ = 14,000 μg/l

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Table 9. Marine invertebrate acute values for nickel

| Organism | Bioassay Method* | Test Conc.** | Time (hrs) | LC50 (ug/l) | Adjusted LC50 (ug/l) | Reference |
|---|---|---|---|---|---|---|
| Sandworm,<br>*Nereis virens* | S | U | 96 | 25,000 | 21,175 | Eisler & Hennekey, 1977 |
| Cockle,<br>*Cardium edule* | S | U | 48 | 500,000 | 182,105 | Portmann, 1968 |
| Cockle,<br>*Cardium edule* | S | U | 48 | 330,000 | 120,189 | Portmann, 1972 |
| Atlantic oyster (larva),<br>*Crassostrea virginica* | S | U | 48 | 1,180 | 999 | Calabrese, et al. 1973 |
| Hard clam (larva),<br>*Mercenaria mercenaria* | S | U | 48 | 310 | 262 | Calabrese & Nelson, 1974 |
| Soft shell clam,<br>*Mya arenaria* | S | U | 96 | 320,000 | 271,040 | Eisler & Hennekey, 1977 |
| Copepod,<br>*Acartia clausi* | S | U | 96 | 2,850 | 2,414 | U.S. EPA, 1974 |
| Stone crab,<br>*Carcinus maenas* | S | U | 48 | 300,000 | 109,263 | Portmann, 1968 |
| Brown shrimp,<br>*Crangon crangon* | S | U | 48 | 150,000 | 54,631 | Portmann, 1968 |
| Brown shrimp,<br>*Crangon crangon* | S | U | 48 | 100,000 | 36,421 | Portmann, 1972 |
| Crab,<br>*Pagurus longicarpus* | S | U | 96 | 47,000 | 39,809 | Eisler & Hennekey, 1977 |
| Shrimp,<br>*Pandalus montagui* | S | U | 48 | 200,000 | 72,842 | Portmann, 1968 |
| Snail,<br>*Nassarius obsoletus* | S | U | 96 | 72,000 | 60,984 | Eisler & Hennekey, 1977 |
| Starfish,<br>*Asterius forbesi* | S | U | 96 | 150,000 | 127,050 | Eisler & Hennekey, 1977 |

Table 9. (Continued)

| Organism | Bioassay Method | Test Conc. | Time (hrs | LC50 (µg/l) | Adjusted LC50 (µg/l) | Reference |
|---|---|---|---|---|---|---|

* S = static
** U = unmeasured
Geometric mean of adjusted values = 24,970 µg/l $\frac{24,970}{49}$ = 510 µg/l

Table 10. Marine plant effects for nickel

| Organism | Effect | Concentration (µg/l) | Reference |
|---|---|---|---|
| Giant kelp,<br>*Macrocystis pyrifera* | 50% inactivation of photosynthesis | 2,000 | Clendenning & North, 1959 |
| Alga,<br>*Phaeodactylum tricornutum* | Reduced growth | 1,000 | Skaar, et al. 1974 |

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Lowest Plant Value = 1,000 µg/l

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Table 11. Other marine data for nickel

| Organism | Test Duration | Effect | Result (ug/l) | Reference |
|---|---|---|---|---|
| Winter flounder, *Pseudopleuronectes americanus* | 96 hrs | LC50 | >33,000 | U.S. EPA, 1975a |
| Mummichog, *Fundulus heteroclitus* | 72 hrs | LC50 | >50,000 | U.S. EPA, 1973 |
| Soft-shell clam, *Mya arenaria* | 48 hrs | LC50 | >50,000 | U.S. EPA, 1975b |
| Sea urchin (embryo), *Lytechinus pictus* | 20 hrs | Delayed development | 58 | Timourian & Watchmaker, 1972 |
| Sea urchin (embryo), *Lytechinus pictus* | 20 hrs | Abnormal development | 580 | Timourian & Watchmaker, 1972 |
| Sea urchin (embryo), *Arbacia punctulata* | 42 hrs | >50% embryo mortality | 17,000 | Waterman, 1937 |

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# NICKEL

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## Mammalian Toxicology and Human Health Effects

### EXPOSURE

Assessment of the risk posed by nickel to public health in the United States entails consideration of two general facets of the issue: sources of exposure relevant to U.S. populations at large and population response.

Some obvious questions about the exposure aspects of nickel are: (1) What are the environmental sources of nickel in the United States? (2) What are the various routes by which nickel enters the body?

Nickel, in common with other metallic elements, is a multimedia contaminant. Thus, one needs to have a clear understanding of fractional contributions on total body burden in humans through various routes of exposure before one can assess the relative significance of any given avenue of intake. A second complicating factor is the impact of a primary route of environmental entry on other compartments of the environment. For example, to what degree does airborne nickel contribute to contamination of water and soil via fallout?

Some aspects of the problem of human population response to nickel include: (1) the relevant human biological and pathophysiological responses to nickel; (2) subgroups of the U.S. population that can be identified as being at particular risk to effects of nickel by virtue of either exposure setting or some physiological status imparting heightened vulnerability; (3) the magnitude of the risk to these subgroups in terms of the numbers exposed and as can best be determined by available population data.

A discussion of the various effects of nickel on man includes dose-effect and dose-response relationships and the various parameters that are of utility in assessing both magnitude of exposure and the extent of response.

"Dose" is the amount or concentration of a substance which is presented over a defined time to the specific site where a given effect is elicited. In man, it is rarely feasible to assess this directly, and one must depend on some other means which reflects the target-site level of the toxicant. Usually, one must select levels of the agent in urine, blood, hair, etc. as indices of internal exposure, and these levels are integrated reflections of the total contributions from various external exposures.

"Effect" is a physiological change resulting from exposure to a toxic substance, while "adverse health effect" is taken to mean an impairment of either the organism's ability to function optimally or the organism's reserve capacity to cope with other systemic stresses.

A dose-effect relationship is a quantitative statement of the relationship between changes in the quantity of an agent and observed gradations of severity in effect resulting therefrom. Dose-response refers to the frequency with which a given effect occurs within a population at a defined dose.

Furthermore, Nordberg (1976) has defined the concept of critical organ, critical concentration and critical effect. "Critical organ" is that organ which first obtains the critical concentration of a metal under defined conditions. "Critical concentration" is that mean concentration of the toxicant in the critical organ at which adverse effects are first manifested. That point in the dose-effect relationship at which an adverse effect exists is termed the "critical effect."

Nickel enters the environment via both natural and anthropogenic activity, and a detailed description of sources and prevalence of nickel in the environment is given in the comprehensive National Academy of Sciences (NAS) review (Natl. Acad. Sci., 1975).

In 1972, U.S. consumption of nickel, exclusive of scrap, was estimated to total about 160,000 tons (Reno, 1974). The estimate consisted mainly of commercially pure nickel (about 110,000 tons). The main uses for this commercially pure nickel were stainless steel, various other alloys, and electroplating. Presumably, the commercial utility of nickel is such that growth in the use of nickel is assured.

From the total consumption of nickel in the United States, it is difficult to determine what fraction of each of the end uses is dissipated into the environment in ways that are relevant to general population exposure assessment. Similarly, the relative contribution of naturally emitted nickel cannot be precisely stated, although the relative impact of this source is not as great as that arising from man's activities.

The approach taken in this document is to give attention to the various media by which the general population comes into contact with nickel and to define the nickel levels therein: ambient air, water, foodstuffs, soil, and other exposure sources.

## Ingestion from Water

The values for nickel levels in 969 U.S. public water supplies for 1969-1970 are presented in Table 1. The survey includes eight metropolitan areas (Natl. Acad. Sci., 1975). The average value, taken at the consumer tap, was 4.8 μg/l, with only 11 systems of this total exceeding 25 μg/l. The highest level was in one supply, 75 μg/l.

Since the data in Table 1 do not furnish any measure of the number of people consuming drinking water of variable nickel content, the nickel levels for water supplies of the 10 largest U.S. cities have been listed in Table 2. This table is based on the data of Durfor and Becker (1964).

## TABLE 1. NICKEL LEVELS IN U.S. DRINKING WATER, 1969-1970[a]

| Ni concn, mg/l. | No. of samples | Ni frequency (percent of samples) |
|---|---|---|
| 0.000 | 543 | 21.69 |
| 0.001-0.005 | 1,082 | 43.22 |
| 0.006-0.010 | 640 | 25.57 |
| 0.011-0.015 | 167 | 6.68 |
| 0.016-0.020 | 46 | 1.84 |
| 0.021-0.025 | 14 | 0.56 |
| 0.026-0.030 | 4 | 0.16 |
| 0.031-0.035 | 2 | 0.08 |
| 0.036-0.040 | 1 | 0.04 |
| 0.041-0.045 | 1 | 0.04 |
| 0.046-0.050 | 1 | 0.04 |
| 0.051-0.055 | 1 | 0.04 |
| 0.075 | 1 | 0.04 |
| Total | 2,503 | 100.00 |

[a] Samples from 969 water systems. Data from Natl. Acad. Sci. (1975).

## TABLE 2. NICKEL LEVELS OF DRINKING WATER OF 10 LARGEST U.S. CITIES[a]

| City | Nickel level, μg/l. |
|---|---|
| New York City | 2.3[b] |
| Chicago | 7.4[c] |
| Los Angeles | 4.8[b] |
| Philadelphia | 13.0[b] |
| Detroit | 5.6[b] |
| Houston | 4.5[c] |
| Baltimore | 4.7[c] |
| Dallas | 5.2[c] |
| San Diego | <7.8 |
| San Antonio | Not detected |

[a] Tabulation adapted from Natl. Acad. Sci. (1975); values for 1962 survey of Durfor and Becker (1964).

[b] In storage.

[c] Post-treatment.

The values for New York City, Chicago, and Los Angeles do not appear to be markedly at variance with the value of 4.8 µg/l. from Table 1.

Ingestion from Food

The route by which most people in the general population receive the largest portion of daily nickel intake is through foods.

The assessment of average daily nickel intake in food can be done either by considering the aggregate nickel content of average diets in the population or by fecal nickel determinations. Although fecal nickel levels would be more meaningful than diet analysis, given the very small gastrointestinal absorption of nickel in man, such data have been sparse in the literature in terms of representative groups of individuals.

Some representative nickel values for various foodstuffs, adapted from data in the NAS Nickel Report, are given in Table 3. These values have been obtained by different laboratories using different methods and may be dated in some cases. Total daily dietary intake values may range up to 900 µg nickel, depending on the nature of the diet, with average values of 300 to 500 µg daily. Total daily dietary intake values may range up to 900 µg nickel, depending on the nature of the diet, with average values of 300 to 500 µg daily (Natl. Acad. Sci., 1975).

Schroeder et al. (1962) calculated an average oral nickel intake by American adults of 300 to 600 µg/day, while Louria and co-workers (1972) arrived at a value of 500 µg/day. Murthy et al. (1973) calculated the daily food nickel intake in institutionalized children, 9 to 12 years old, from 28 U.S. cities at an average value of 451 µg/day. In a related study, Myron et al. (1978) determined the nickel content of nine institutional diets in the U.S. and calculated an average intake of 165 µg/day.

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## TABLE 3. NICKEL CONTENT OF VARIOUS CLASSES OF FOODS IN U.S. DIET[a]

| Food class and examples | Nickel content, ppm, wet weight |
|---|---|
| Grains/grain products | |
| Wheat flour, all-purpose | 0.54 |
| Bread, whole-wheat | 1.33 |
| Corn, fresh frozen | 0.70 |
| Rice, polished American | 0.47 |
| Rye flour | 0.23 |
| Rye bread | 0.21 |
| Fruits and vegetables | |
| Potatoes, raw | 0.56 |
| Peas, fresh frozen | 0.30 |
| Peas, canned | 0.46 |
| Beans, frozen | 0.65 |
| Beans, canned | 0.17 |
| Lettuce | 0.14 |
| Cabbage, white | 0.32 |
| Tomatoes, fresh | 0.02 |
| Tomato juice | 0.05 |
| Spinach, fresh | 0.35 |
| Celery, fresh | 0.37 |
| Apples | 0.08 |
| Bananas | 0.34 |
| Pears | 0.20 |
| Seafood | |
| Oysters, fresh | 1.50 |
| Clams, fresh | 0.58 |
| Shrimp | 0.03 |
| Scallops | 0.04 |
| Crabmeat, canned | 0.03 |
| Sardines, canned | 0.21 |
| Haddock, frozen | 0.05 |
| Swordfish, frozen | 0.02 |
| Salmon | 1.70 |
| Meats | |
| Pork (chops) | 0.02 |
| Lamb (chops) | Not detected |
| Beef (chuck) | Not detected |
| Beef (round) | Not detected |

[a] Adapted from Natl. Acad. Sci. (1975).

Food processing methods apparently add to the nickel levels already present in foodstuffs via (1) leaching from nickel-containing alloys in food-processing equipment made from stainless steel, (2) the milling of flour, and (3) catalytic hydrogenation of fats and oils by use of nickel catalysts.

Several studies have reported daily fecal excretions of nickel. Nodiya (1972) reported a fecal excretion average of 258 µg in Russian students. Horak and Sunderman (1973) determined fecal excretions of nickel in 10 healthy subjects and arrived at a value of 258 µg/day, identical to the Russian study.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. Since BCFs are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the average per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey, the relative consumption of the four major groups can be calculated.

A mean measured bioconcentration factor of 61 was obtained for fathead-minnow larvae (Lind, et al. Manuscript) based on whole body measurements after a 28-day exposure to nickel. The values were corrected for nickel in the control organisms and corrected from dry weight to wet weight. Based on data for lead and cadmium, nickel would probably have a lower BCF for fish and decapod muscle than for fish whole body, but probably would have a higher BCF for molluscs.

| Group | Consumption (Percent) | Bioconcentration Factor |
|---|---|---|
| Freshwater fishes | 12 | 6 |
| Saltwater fishes | 61 | 6 |
| Saltwater molluscs | 9 | 70 |
| Saltwater decapods | 18 | 6 |

Using the data for consumption and estimated bioconcentration factors for each of these groups, the weighted average BCF for nickel is 11 in consumed fish and shellfish.

Inhalation

Perhaps the most comprehensive assessment of ambient air levels of nickel in the U.S. is that of the National Air Surveillance Network. Tabulation of air nickel levels for the period 1964 through 1969 are contained in the NAS Nickel Report (Nickel. NAS, 1975) for 231 urban and 47 nonurban localities. More recent figures are available for the period 1970-1974 (EPA, 1976).

Table 4 tabulates the air nickel averages for urban stations for the period 1970-1974. For 1974, the most recent entry, the arithmetic mean level was 9 $ng/m^3$.

Table 5 presents the corresponding values for all nonurban stations for the same period. Again for 1974, the arithmetic mean level was 2 $ng/m^3$.

It may be seen from Tables 4 and 5 as well as earlier surveys in the NAS Nickel Report, that there is a clear difference in urban versus nonurban nickel levels, with urban values being around three- to four-fold higher.

Trends in air metal level changes for urban and nonurban areas have been assessed for a number of elements including nickel (Faoro and McMullen, 1977).

### TABLE 4. URBAN CUMULATIVE FREQUENCY DISTRIBUTIONS OF AMBIENT AIR NICKEL LEVELS[a]

| Year | No. of sites | Percentile Min. | 10 | 50 | 99 | Arithmetic Mean (SD) | |
|---|---|---|---|---|---|---|---|
| 1970 | 797 | 0.001 | 0.001 | 0.001 | 0.127 | 0.015 | (0.028) |
| 1971 | 717 | 0.001 | 0.001 | 0.001 | 0.126 | 0.015 | (0.028) |
| 1972 | 708 | 0.001 | 0.001 | 0.001 | 0.100 | 0.011 | (0.023) |
| 1973 | 559 | 0.001 | 0.001 | 0.001 | 0.133 | 0.014 | (0.037) |
| 1974 | 594 | 0.001 | 0.001 | 0.001 | 0.057 | 0.009 | (0.029) |

[a] Contracted tabulation from U.S. EPA data (1976), Table 4.1.

[b] Values under given percentile indicate the percentage of stations below air level. Values in μg/m$^3$.

### TABLE 5. NONURBAN CUMULATIVE FREQUENCY DISTRIBUTIONS OF AMBIENT AIR NICKEL LEVELS[a]

| Year | No. of sites | Percentile Min. | 10 | 50 | 99 | Arithmetic mean (SD) | |
|---|---|---|---|---|---|---|---|
| 1970 | 124 | 0.001 | 0.001 | 0.001 | 0.076 | 0.005 | (0.024) |
| 1971 | 97 | 0.001 | 0.001 | 0.001 | 0.046 | 0.003 | (0.011) |
| 1972 | 137 | 0.001 | 0.001 | 0.001 | 0.076 | 0.004 | (0.012) |
| 1973 | 100 | 0.001 | 0.001 | 0.001 | 0.188 | 0.011 | (0.037) |
| 1974 | 79 | 0.001 | 0.001 | 0.001 | 0.020 | 0.002 | (0.004) |

[a] Contracted tabulation from U.S. EPA data (1976), Table 4.2.

[b] Values under given percentile indicate the percentage of stations below the given air value. Values in μg/m$^3$.

Figure 1 depicts the trend in the 50th percentile at urban sites of annual air nickel averages for the period 1965-1974. Nickel shows a downward trend over this period, being most pronounced in the latter half of the survey period with an approximate drop of 40 percent from the 1970-71 to the 1973-74 values. Nickel is one of the metals associated with fuel combustion, particularly oil. This relationship is based on documented season-dependent gradients in air levels with highest levels in the winter quarter when space heating is at a maximum.

Sulfur regulations which have been in effect over the period 1965-1974 appear to be the major factor in lower air nickel levels, particularly in the northeastern United States. Sulfur removal from residual oil necessitated by these regulations indirectly removes nickel as well (Faoro and McMullen, 1977).

How long this trend to lower air nickel values in urban areas will continue, in view of the above, will depend primarily on the future status of sulfur regulations as well as the level of fuel oil consumption.

### Dermal

The discussion of nickel exposure routes so far has focused on intake and systemic absorption from various media: air, food, and water. External contact with nickel is associated with clinically defined skin disorders. There is an extensive list of commodities which contain nickel and through which the general population can be externally exposed. In particular, the use of stainless steel kitchens, nickel-plated jewelry, and various other nickel-containing materials has created a widespread problem for nickel-sensitive individuals.

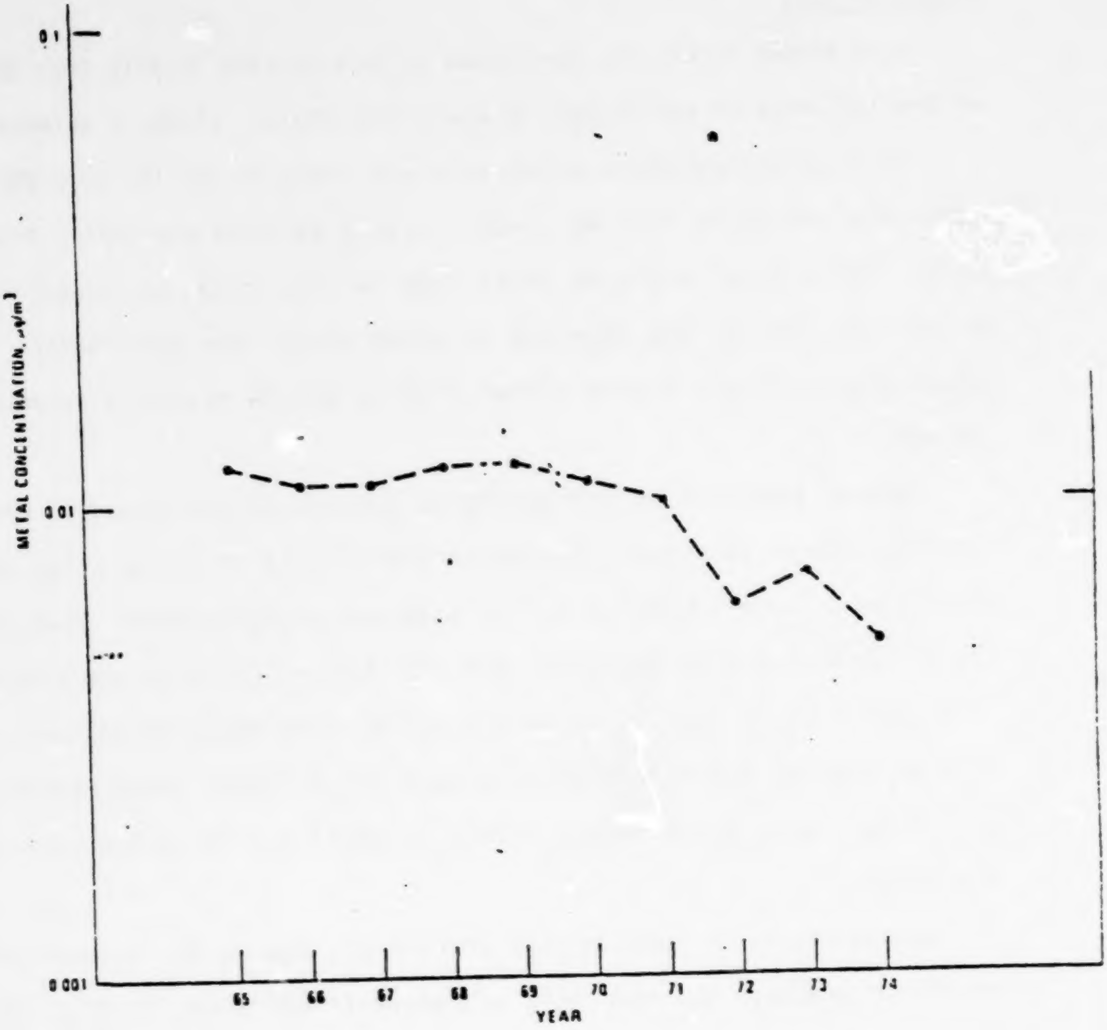

Figure 1. Trend in the 50th percentile at urban sites of average for nickel. From Faoro and McMullen (1977).

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## Other Sources of Exposure

### Nickel in Soil

Soil nickel levels are considered in this section chiefly from the aspect of the influence of soil nickel on man's food chain: plants → animals → man.

Soils normally contain nickel in a wide range of levels, 5 to 500 ppm and soils from serpentine rock may contain as much as 5,000 ppm (Natl. Acad. Sci., 1975). While these levels may appear high in some instances, nickel content of soils as such is less important for plant uptake than such factors as soil composition, soil pH, organic matter in soil, and the classes of plants grown therein.

Natural levels of soil nickel may be added to by contamination from human activity such as atmospheric fallout in the areas of nickel-emitting industrial activities or auto traffic as well as treatment of agricultural lands with nickel-containing super phosphate fertilizers or municipal sewage sludge.

Ragaini et al. (1977), in their study of trace metal contaminants of soil and grasses near a lead-smelting operation in Idaho, found that surface soil nickel levels are enriched 39-fold in sampling sites in the vicinity of the smelter.

Contamination of roadside soil with nickel, leading to increased nickel content of grasses, has been noted by Lagerwerff and Specht (1970). There was an increase in grass nickel levels from 1.3 to 3.8 ppm dry weight, dependent on the distance from the roadside. Sources of roadside nickel were presumed by the authors to arise from fuel combustion as well as from external abrasion of nickel from auto parts.

In a study on the uptake of nickel by the edible portions of food crops such as bush beans, cabbage, onions, tomatoes, and potatoes grown in test pots in municipal sludge from Ithaca, N.Y., Furr et al. (1976) observed: (1) at first-year harvest, nickel levels in the above food crops were increased two-to-threefold compared to control soil, the corresponding soil pH levels being 7.1 for sludge-amended samples and 5.3 for control soils; (2) at second harvest, the increases seen in the first harvest did not recur, except for about a twofold increase in onions and tomatoes.

John and Van Laerhoven (1976) determined the effect of applying sludge at various loading rates on trace metal uptake by romaine lettuce and beets grown on amended soil with and without liming. Sludge used with unlimed soil significantly increased nickel levels in lettuce, did not affect the element level in beet tops, and reduced the nickel content of beet tubers. On the other hand, liming led to increases of nickel in all plant tissues at a 25 g/kg loading rate for one type of sludge (Milorganite) but not with a second type produced at a local treatment plant.

### Cigarette Smoke

Cigarette smoking can contribute significantly to man's daily nickel intake by inhalation and nickel from this source probably exceeds the amount absorbed by breathing ambient air. An individual smoking two packs of cigarettes a day would inhale 1 to 5 mg of nickel per year or about 3 to 15 μg nickel daily. The possible existence of nickel in cigarette smoke as nickel carbonyl suggests that there would be a net daily absorption of about 1.5 to 7.5 μg into the bloodstream. This may be contrasted to the markedly smaller amounts taken in by inhalation of nickel in ambient air (vide supra).

## PHARMACOKINETICS

Routes of nickel intake for man and animals are inhalation, ingestion, and percutaneous absorption. Parenteral exposure is mainly of importance in experimental animal studies.

The relative amount of inhaled nickel which is absorbed from various compartments of the pulmonary tract is a function of both chemical and physical forms. Pulmonary absorption into the blood stream is probably greatest for nickel carbonyl vapor, with animal studies suggesting that about half of the inhaled amount is absorbed. Nickel in particulate matter is absorbed from the pulmonary tract to a considerably lesser degree than nickel carbonyl. Smaller particles are lodged deeper in the respiratory tract and the relative absorption is greater than with larger particles. Lung model and limited experimental data suggest several percent absorption. While insoluble nickel compounds may undergo limited absorption from the respiratory tract, their relative insolubility has implications for the carcinogenic character of nickel, as will be noted below.

Absorption from the gastrointestinal tract of dietary nickel is on the order of 1 to 10 percent in man and animals from both foodstuffs and beverages.

Percutaneous absorption of nickel occurs and is related to nickel-induced hypersensitivity and skin disorders. The extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time.

Absorbed nickel is carried by the blood, although the extent or partitioning between erythrocyte and plasma cannot be precisely stated. In any event,

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plasma or serum levels reflect the blood burden. Normal serum nickel values in man are 2 to 3 μg/l. Albumin is the main macromolecular carrier of nickel in a number of species, including man. In man and rabbit, there also appear to be nickel-specific proteins.

Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in lung, brain, kidney, liver, and adrenals. Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver, and lung.

Based on animal studies, nickel appears to have a half-time of several days in the body. There is little evidence for tissue accumulation.

The main excretory route of absorbed nickel in man and animals appears to be through the urine, with biliary excretion also occurring in experimental animals. While hair deposition of nickel also appears to be an excretory mechanism, the relative magnitude of this route, compared to urinary excretion, is not fully known at present.

A number of disease states or other physiological stresses can influence nickel metabolism in man. In particular, heart and renal disease, burn trauma, and heat exposure can either raise or lower serum nickel levels.

## Absorption

The major routes of nickel absorption are inhalation and ingestion via the diet. Percutaneous absorption is a less significant factor for nickel's systemic effects but important in the allergenic responses to nickel. Parenteral administration of nickel is mainly of interest to experimental studies and particularly helpful in the assessment of the kinetics of nickel transport, distribution, and excretion in addition to maximizing the physiological parameters for nickel's effects.

The amounts of nickel absorbed by organisms are determined not only by the quantities inhaled or ingested, but also by the chemical and physical forms of nickel. Other factors, such as host organism nutritional and physiological status, also play a role, but this has been little studied outside of investigations directed at an essential role for nickel.

Gastrointestinal intake of nickel by man is surprisingly high, relative to other toxic elements, which is at least partly accounted for by contributions of nickel from utensils and equipment in processing and home preparation of food.

Collectively, the data of Tedeschi and Sunderman (1957), Perry and Perry (1959), Nomoto and Sunderman (1970), Nodija (1972), and Horak and Sunderman (1973) indicate that 1 to 10 percent of dietary nickel is absorbed.

One question that arises in considering the dietary intake and absorption of toxic elements has to do with the bioavailability of the agent in solid foodstuffs versus water and beverages. Ho and Furst (1973) observed that intubation of 63 Ni in dilute acid solution leads to 3 to 6 percent absorption of the radio-labeled nickel regardless of the dosing level. It does not appear, then, that nickel in simple aqueous solution is absorbed to any greater extent than that incorporated into the matrix of foodstuffs.

Percutaneous absorption of nickel is mainly viewed as important in the dermatopathological effects of this agent, such as contact dermatitis, and absorption viewed this way is restricted to the passage of nickel past the outermost layers of skin deep enough to bind with apoantigenic factors.

Wells (1956) demonstrated that divalent nickel penetrates the skin at sweat-duct and hair-follicle ostia and binds to keratin. Using cadaver skin,

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Kolpokov (1963) found that nickel (II) accumulated in the malpighian layer, sweat glands, and walls of blood vessels. Spruitt et al. (1965) have shown that nickel penetrates to the dermis.

Values for the amounts of nickel passing through outer layers of skin relative to amounts applied have not been determined. Samitz and Pomerantz (1958) have reported that the relative extent of nickel penetration is enhanced by sweat and detergents.

Mathur and co-workers (1977) have reported the systemic absorption of nickel from the skin using nickel sulfate at very high application rates. After 30 days of exposure to nickel at doses of 60 and 100 mg Ni/kg, a number of testicular lesions were observed in rats, while hepatic effects were seen by 15 days at these exposure levels. It is not possible to calculate any absorption data from this study.

Respiratory absorption of various forms of nickel is probably the major route of nickel entry into man under conditions of occupational exposure. Of these forms, nickel carbonyl is one that has been found to be toxic.

Nickel carbonyl, $Ni(CO)_4$, is a volatile, colorless liquid (b.p. 43°C), Armit (1908) judged its relative toxicity to be a hundred fold higher than that of carbon monoxide. More recently, the threshold limit value (TLV) for a work day exposure has been set at 50 parts per billion (ppb). In contrast, the corresponding value for hydrogen cyanide is 10 parts per million (ppm), 200-fold greater (Am. Conf. of Gov. Ind. Hyg., 1971). The presence and toxicological history of $Ni(CO)_4$ as a workplace hazard followed closely upon the development of the Mond process of nickel purification in its processing (Mond et al., 1890). A detailed discussion of the toxicological aspects of nickel carbonyl poisoning is included in the NAS Report on Nickel (1975) as well as a recent review by Sunderman (1977).

Studies of nickel carbonyl metabolism by Sunderman and co-workers (Sunderman and Selin, 1968; Sunderman et al., 1968) indicate that pulmonary absorption is both rapid and extensive, the agent passing the alveolar wall as $Ni(CO)_4$ intact. Sunderman and Selin (1968) observed that rats exposed to nickel carbonyl at 100 mg Ni/l air for 15 minutes excreted 26 percent of the inhaled amount in the urine by 4 days postexposure. On taking into account the exhaled quantity, as much as half of the inhaled amount could have been initially absorbed.

Few data on the pulmonary absorption of nickel from particulate matter deposited in the lung exist. The International Radiological Protection Commission Task Group on Lung Dynamics (1966) has advanced detailed deposition and clearance models for inhaled dusts of whatever chemical origin as a function of particle size, chemical properties, and compartmentalization within the pulmonary tract. Nickel oxide and nickel halides are classified as Class W compounds, i.e., compounds having moderate retention in the lungs and a clearance rate from the lungs of weeks in duration.

While the model described above has limitations, it can be of value in approximating deposition and clearance rates for nickel compounds of known particle size. For example, Natusch et al. (1974) based on a detailed study of eight coal-fired power plants, found that nickel is one of a number of elements emitted from these sources that is found in the smallest particles of escaped fly ash, about 1 to 2 μm mass median aerodynamic diameter (MMAD), this being a size that penetrates deepest into the pulmonary tract. According to the approaches of the IRPC model, particles of 1 μm undergo a total deposition percentage of 63 percent, with 30 percent in the nasopharyngeal tract, 8 percent in the tracheobronchial part, and 25 percent in the pulmonary compartment. The clearance rate of deposited particulate matter in the IRPC model is based on chemical homogeneity of the particulates, however, and one can only approximate such clearance if heterogeneous particles are considered. According to Natusch et al. (1974), nickel-enriched particles in fly ash have much of the nickel on the particle surface. If one approximates the clearance rate by assuming that particles enriched in nickel in the outer portions of the particle are handled by the model lung in a fashion similar to a homogenous particle of, say, nickel, then one obtains a total approximate absorption (clearance) of about 6 percent, with major clearance calculated as taking place from the pulmonary compartment, 5 percent.

Wehner and Craig (1972), in their studies of the effect of nickel oxide aerosols on the golden hamster, observed that inhalation by these animals of nickel oxide particles in a concentration of 2 to 160 μg/l (2 to 160 $mg/m^3$) and particle size of 1.0 to 2.5 μm MMAD led to a deposition of 20 percent of the total amount inhaled. After 6 days postexposure, 70 percent of the nickel oxide remained in the lungs, and even after 45 days approximately half the original deposition was still present. Since no material increase in nickel levels of other tissues had occurred, it appeared that absorption in this interval was negligible. In a later, related study (Wehner et al., 1975), co-inhalation of cigarette smoke showed no effect on either deposition or clearance.

Leslie and co-workers (1976) have described their results with exposure of rats to nickel and other elements contained in welding fumes. In this case, the particle size vs. nickel content was known precisely, highest nickel levels being determined in particles 0.5 to 1.0 μm in diameter at an air level of 8.4 μm Ni/m$^3$. While the authors did not determine the total nickel deposition in the lungs of these animals, they observed that essentially no clearance of the element from the lung had occurred by 24 hours, nor were there elevations in blood nickel, suggesting negligible absorption. In contrast, Graham et al., (1978), using nickel chloride aerosol and mice ($\leq 3$ μm diameter, 110 μg Ni/m$^3$) found about 75 percent clearance by day 4 postexposure. The rapid clearance of the nickel halide was probably due to its solubility relative to the oxide.

In addition to nickel exposure in man due to inhalation of ambient and workplace air, cigarette smoking constitutes a possible significant source among heavy smokers. Studies by Sunderman and Sunderman (1961a), Szadkowski and co-workers (1969), and Stahly (1973) indicate that 10 to 20 percent of cigarette nickel is carried in mainstream smoke, with better than 80 percent of this amount being in gaseous, rather than particulate, form. Since it is quite possible that nickel carbonyl constitutes the gaseous fraction (Sunderman and Sunderman, 1961a), one must assume that the relative absorption of nickel from cigarette smoke is proportionately greater than from airborne nickel particulates and with heavy smokers may be the main source of inhalatory nickel absorbed. Individuals smoking two packs of cigarettes daily can inhale up to 5 mg nickel annually (Natl. Acad. Sci., 1975). By contrast, an individual in an urban U.S. area having an air level of Ni of 0.025 μg/m$^3$ (Natl. Acad. Sci., 1975 for regional average values of airborne nickel) and breathing 20 m$^3$ daily would inhale somewhat less than 0.2 mg. The relative significance for absorption would be even greater (vide supra).

## Distribution

The kinetic processes governing the transport and distribution of nickel in various organisms are dependent upon the modes of absorption, the rate and level of nickel exposure, the chemical form of nickel and the physiological status of the organism.

Blood is the main vehicle for transport of absorbed nickel. While it is difficult to determine from the literature the exact partitioning of nickel between erythrocytes and plasma or serum for unexposed individuals, serum levels are rather good reflections of blood burden and exposure status (Natl. Acad. Sci., 1975). In unexposed individuals, serum nickel values are approximately 0.2-0.3 µg/dl.

Distribution of serum-borne nickel among the various biomolecular components has been discussed in some detail in a recent review (Natl. Acad. Sci., 1975), and it will mainly be noted here that serum albumin is the main carrier protein in sera of man, the rabbit, the rat, and bovines. Furthermore, there exists in sera of man and rabbits a nickel-rich metalloprotein identified as an $\alpha_1$-macroglobulin (nickeloplasmin) in rabbits and in man as a 9.5 S $\alpha_1$-glycoprotein. Sunderman (1977) has suggested that nickeloplasmin may be a complex of the $\alpha_1$-glycoprotein with serum $\alpha_1$-macroglobulin.

While the relative amounts of protein-bound nickel in sera of various species have a considerable range (Hendel and Sunderman, 1972) which reflect relative binding strengths of albumins, the total nickel levels are markedly similar, as may be seen in Table 6.

A number of studies of the distribution of nickel in experimental animals exposed to nickel carbonyl have been described (Natl. Acad. Sci., 1975).

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TABLE 6. SERUM NICKEL IN HEALTHY ADULTS OF SEVERAL SPECIES[a]

| Species (N) | Nickel concentration, µg/l[b] |
|---|---|
| Domestic horse (4) | 2.0 (1.3-2.5) |
| Man (47) | 2.6 (1.1-4.6) |
| Jersey cattle (4) | 2.6 (1.7-4.4) |
| Beagle dog (4) | 2.7 (1.8-4.2) |
| Fischer rat (11) | 2.7 (0.9-4.1) |
| British goat (3) | 3.5 (2.7-4.4) |
| New Hampshire chicken (4) | 3.6 (3.3-3.8) |
| Domestic cat (3) | 3.7 (1.5-6.4) |
| Guinea pig (3) | 4.1 (2.4-7.1) |
| Syrian hamster (3) | 5.0 (4.2-5.6) |
| Yorkshire pig (7) | 5.3 (3.5-8.3) |
| New Zealand rabbit (24) | 9.3 (6.5-14.0) |
| Main lobster (4) | 12.4 (8.3-20.1) |

[a] From Sunderman et al. (1972a)

[b] Mean (and range)

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Armit (1908) exposed dogs, cats, and rabbits to nickel carbonyl vapor and was able to measure elevated nickel levels in lung, brain, kidney, and adrenal glands. Later investigators have observed elevated, rapidly cleared levels of nickel in lungs, brain, kidney, and liver of various animal species (Barnes and Denz, 1951; Sunderman et al., 1957; Ghiringhelli and Agamennone, 1957; Sunderman and Selin, 1968; Mikheyev, 1971).

Sunderman and Selin (1968) have shown that one day after exposure to inhaled ($^{63}$Ni) - nickel carbonyl, viscera contained about half of the total absorbed label with one-third in muscle and fat. Bone and connective tissue accounted for about one-sixth of the total. Spleen and pancreas also appear to take up an appreciable amount of nickel. Presumably, nickel carbonyl crosses the alveolar membrane intact from either direction, inhalation or injection, suggesting that its stability is greater than has usually been assumed (Kasprzak and Sunderman, 1969; Sunderman et al., 1968; Sunderman and Selin, 1968). Retained nickel carbonyl undergoes decomposition to carbon monoxide and nickel of zero valency in the erythrocyte and tissues, followed by intracellular oxidation of the element to the divalent form with subsequent release into serum.

In human subjects acutely exposed to nickel carbonyl vapor, highest nickel levels were found in the lung, followed by kidney, liver, and brain (Natl. Acad. Sci., 1975).

A number of reports in the literature describe the tissue distribution of divalent nickel following parenteral administration of nickel salts. These studies have been of two types: tissue nickel content assessment or studies measuring the kinetics of nickel deposition and clearance within a modeling framework. These data are summarized in Table 7.

TABLE 7. TISSUE DISTRIBUTION OF NICKEL (II) AFTER PARENTERAL ADMINISTRATION[a]

| Species | N | Dosage[a] | Relative distribution of $^{63}Ni$ | Reference |
|---|---|---|---|---|
| Mouse | 8 | 6.2 mg/kg (one intraperitoneal injection) | Kidney > lung > plasma > liver > erythrocyte spleen > bladder > heart > brain > carcass (muscle, bone, and fat) | Wase et al. (1954) |
| Rat | 4 | 617 µg/kg (one intravenous injection) | Kidney > lung > adrenal > ovary > heart > gastrointestinal tract > skin > eye > pancreas > spleen = liver > muscle > teeth > bone > brain = fat | Smith and Hackley (1968) |
| Guinea pig | 6 | 1 mg/kg (subcutaneously for 5 days) | Kidney > pituitary > lung > liver > spleen > heart > adrenal > testis > pancreas > medulla > oblongata = cerebrum = cerebellum | Clary (1975 |
| Rabbit | 3 | 240 µg/kg (one intravenous injection) | Kidney > pituitary > serum > whole blood > skin > lung > heart > testis > pancreas > adrenal > duodenum > bone > spleen > liver > muscle > spinal cord > cerebellum > medulla oblongata = hypothalamus | Parker and Sunderman 1974) |
| Rabbit | 4 | 4.5 µg/kg (intravenously for 34-38 days) | Kidney > pituitary > spleen > lung > skin > testis > serum = pancreas = adrenal > sclerae duodemun = liver > whole blood > heart > bone > iris > muscle > cornea = cerebellum = hypothalamus > medulla oblongata > spinal cord > retina > lens > vitreous humor | |

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[a] From Natl. Acad. Sci., 1975.

It can be generally stated that nickel administered this way leads to highest accumulation in kidney, endocrine glands, lung, and liver. Relatively little nickel is lodged in neural tissue, consistent with the observed low neurotoxic potential of divalent nickel salts. Similarly, there is relatively slight uptake into bone, consistent with other evidence that nickel is rather rapidly and extensively cleared from organisms, with little retention in soft or mineral tissue.

Onkelinx et al. (1973) studied the kinetics of injected $^{63}$Ni metabolism in rats and rabbits. In both species, a two-compartment model of clearance could be discerned, consisting of fast and slow components. In the rabbit, better than 75 percent of the dose was excreted within 24 hours, while comparable clearance in the rat required 3 days. In a later study, Onkelinx (1977) reported whole body kinetics of $^{63}$Ni in rats. The time course of plasma nickel levels entailed first-order kinetics analyzable in terms of a two-compartment model. The major portion of nickel clearance is accounted for by renal excretion.

Chausmer (1976) has measured exchangeable nickel in the rat using $^{63}$Ni given intravenously. Tissue exchangeable pools were directly estimated and compartmental analysis performed by computer evaluation of the relative isotope retention versus time. Kidney had the largest labile pool within 16 hours with two intracellular compartments. Liver, lung, and spleen pools could also be characterized by two compartments, while bone fit a one-compartment model. Corresponding half-times for the fast and slow components were several hours and several days, respectively.

Oral exposure of experimental animals to nickel with regard to absorption and tissue distribution appears to be dependent upon the relative amounts of the agent employed. Schroeder et al. (1974) could find no uptake of nickel in rats chronically exposed to nickel in drinking water (5 ppm) over the lifetime of the animals. Phatak and Patwardhan (1950) reported the effects of different nickel compounds given orally to rats in terms of tissue accumulation. Among the three chemical forms of nickel used, i.e., carbonate, nickel soaps, and metallic nickel catalyst, tissue levels were greatest in the groups fed the carbonate. O'Dell and co-workers (1971) fed calves supplemental nickel in the diet at levels of 62.5, 250, and 1000 ppm. While levels of nickel were somewhat elevated in pancreas, testis, and bone at 250 ppm, pronounced increases in these tissues were seen at 1000 ppm. Whanger (1973) exposed weanling rats to nickel (acetate) in the diet at levels up to 1000 ppm. As nickel exposure was increased, nickel content of kidney, liver, heart, and testes was also elevated, with greatest accumulation in the kidneys. Spears, et al. (1978) observed that lambs given tracer levels of $^{63}Ni$ orally with or without supplemental nickel in diet had the highest levels of the label in kidney, the relative levels in kidney, lung and liver being less for the low-nickel group.

Comparing the above studies suggests that a homeostatic mechanism exists to regulate low levels of nickel intake, e.g., 5 ppm, but such regulation is overwhelmed in the face of large levels of nickel challenge.

The blood values for nickel, as shown in Table 8, are limited to those utilizing atomic absorption spectrometry. The data are taken from the report by the National Academy of Sciences (1975) and expanded by the addition of three relevant later studies.

The values agree well with the exception of the earliest study, that done by Schaller et al. (1968). The mean value reported for the Høgetveit and Barton study (1976) is of interest, since the authors report in another publication (Høgetveit and Barton, 1977): "These figures today (1977) appear high. There has been a distinct lowering of plasma nickel levels . . . partly due to improved laboratory reliability . . . more recent tests of 21 unexposed adults . . . revealed an average plasma nickel level of 0.21 μg/dl in contrast to the previous control group of 0.42 μg/dl."

Age and sex do not appear to be associated with nickel blood levels, as authors frequently report mean values for the total group only because they have found no significant differences by age or sex. There are no data for this population segment or about lifespan gradient.

Other variables such as race, residence, and geographic location similarly cannot be evaluated, and further, there are no data for "unacculturated" populations who are not exposed to industrial pollution. The only study addressing the question of differences in mean blood nickel levels for normal populations living in environments with differing degrees of pollution due to the absence or presence of nickel refineries is that of McNeely (1972), who examined normal adults who were not occupationally exposed to nickel in Sudbury, Ontario, the location of North America's largest nickel refinery, and compared them to adults from Hartford, Conn. The Sudbury mean serum nickel level for 25 adults was 0.46 ± 0.14 with a range of 0.20 to 0.73 μg/dl, while respective values for Hartford were 0.26 ± 0.09 (range 0.08 to 0.52 μg/dl).

## TABLE 8. "NORMAL" BLOOD NICKEL CONCENTRATIONS

| Author | Method | Area | No. of subjects and sex | Serum (S) or plasma (P) | Nickel concentration of µg/dl | |
|---|---|---|---|---|---|---|
| | | | | | Mean (± SD) | Range |
| Schaller et al. (1968) | Atomic absorption | Germany | 26 | P | 2.1 | 0.6-3.7 |
| Nomoto and Sunderman (1970) | Atomic absorption | Connecticut | 40 | S | 0.26 | 0.11-0.46 |
| McNeely et al. (1972) | Atomic absorption | Connecticut | 26 | S | 0.26 | 0.08-0.52 |
| Pekarek and Hauer (1972) | Atomic absorption | Washington, D.C. | 20 | S | 1.5 (± 0.5) | - |
| Nomoto (1971) | Atomic absorption | Japan | 23 | S | 0.21 (± 0.11) | - |
| Høgetveit (1976) | Atomic absorption | Norway | 3 | P | 0.42 | 0.2-0.6 |
| Spruit (1977) | Atomic absorption | Holland | 10 | P | 0.16 | - |

[a] 86 samples, number of subjects not given.

It should also be noted that smoking status of the individuals tested has not been considered systematically in these reports. The National Academy of Sciences report (1975) cites several studies which showed "that 10 to 20 percent of the nickel in cigarettes is released in the mainstream smoke." The authors conclude that an individual smoking two packs per day may inhale between 1 and 5 mg of nickel a year. There is some evidence that about four-fifths of the nickel in mainstream smoke is in the gaseous phase (Szadkowski et al., 1969). Further, there is inferential evidence that this gaseous nickel is in the form of nickel carbonyl (Kasprzak, 1969; Sunderman, 1968; Stahly, 1973), which has a very high retention in the respiratory tract. It would seem quite possible that regular smoking of one or more packs of cigarettes a day would contribute the major fraction of daily inhaled nickel in the general population.

Data from three studies reporting values of nickel in blood for occupationally exposed persons and nonexposed controls show significant differences. Clausen et al. (1977) report on a study in which atomic absorption spectrometry was used to determine blood nickel levels in a group of Danish garage mechanics as well as a control group of laboratory workers and blood donors. The mean whole blood level of the group of workers was for nickel 5.3 ± 4.8 μg/dl, while the 54 controls showed a mean of 1.7 ± 1.5, range 0.4 to 5.4 μg/dl. The difference was significant at $p < 0.01$.

Høgetveit and Barton (1976) reported on the results of monitoring blood plasma Ni levels in workers in the Falconbridge nickel refinery. They found Ni plasma values of 0.74 μg/dl for 701 samples from 305 workers while controls showed an average value of 0.42 μg/dl in 86 samples. Atomic absorption spectrometry was used in the analyses. The plasma levels for workers at different work stations showed that 179 electrolysis department workers had a mean blood nickel concentration of 0.74 µg/dl while 126 roasting-smelting workers averaged 0.60 µg/dl. Workers engaged in electrolysis operations were found to be exposed to soluble nickel salts in aerosol form while the workers in roasting -smelting operations were exposed to largely insoluble compounds in dust (Høgetveit and Barton, 1977). Figure 2 shows the nickel plasma averages for the two groups of workers as a function of date of initial employment in the industry. Two levels of nickel exposure are evident, as is the finding that levels reflect intensity of exposure and not duration, i.e., blood plasma levels appear to reflect current exposure.

Spruit and Bongaarts (1977a) tested for blood plasma nickel levels in eight occupationally exposed volunteers and found average levels of 1.02 and 1.11 µg/dl at different periods during the work year, but 0.53 µg/dl after the annual two-week holiday. The controls, patients from the dermatology service without occupational exposure, showed plasma levels of 0.16 and 0.20 µg/dl for 10 males and 14 females, respectively. These data support the Høgetveit and Barton (1976) finding that plasma concentrations reflect current exposure and, further, provide evidence that there is very quick response to exposure.

The specific effects on blood levels of nickel of smoking, faulty hygiene, and failure to observe safety regulations among exposed workers have either not been evaluated or, if evaluated, have not been reported. However, there is one case study of a recalcitrant worker (Høgetveit and Barton, 1977) who showed a plasma nickel level of 10.0 µg/dl. Ten days after safety measures were enforced the worker's plasma nickel level had dropped to 3.75 µg/dl and he was given sick leave for 3 weeks. During this leave, the worker's plasma nickel level dropped to 1.0 µg/dl. After he returned to work, his nickel

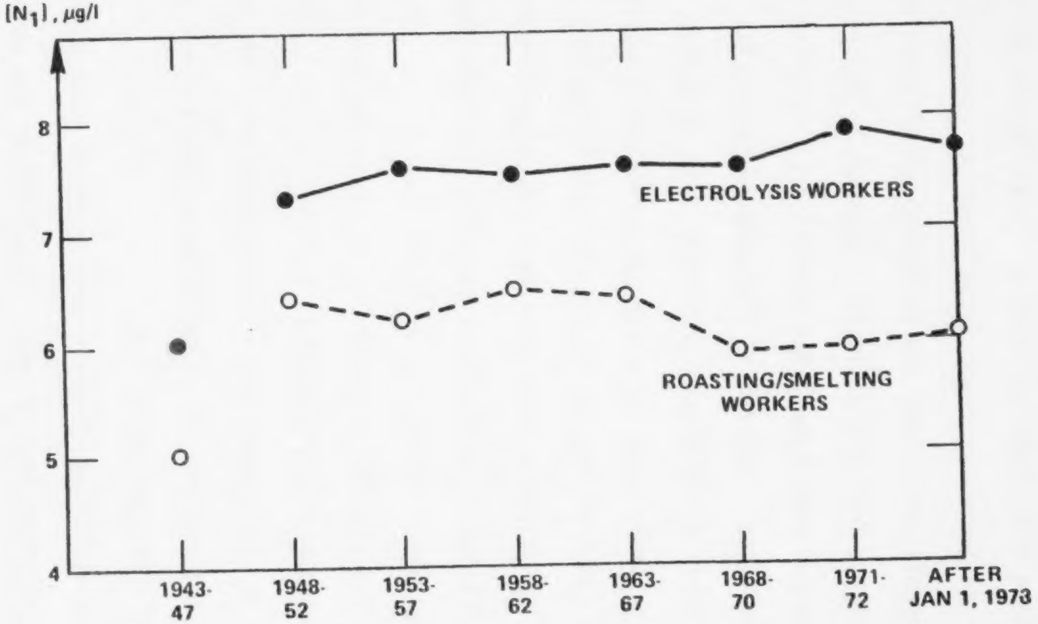

Figure 2. Average plasma nickel levels in employees according to year beginning employment. From Hogeveit and Barton (1976).

level rose steadily until strict safety enforcement brought about a reduction once more.

The data presented for urinary nickel levels are subject to the same strictures as those for blood nickel levels. The analytic technique is subject to considerable error, and the selection of subjects varies from volunteers to clinic patients "not occupationally exposed." The criteria for determining nonexposure and recruitment and selection of volunteers and other "normals" are not specified. Several of the studies evaluating urine nickel concentrations appear in Table 8 for plasma and serum concentrations as well.

The available data for nickel concentrations present a further problem, namely the comparability of values for single samples or 24-hour collections. Spruit and Bongaarts (1977a) reported nickel urine concentrations for different samples collected on consecutive days and found considerable unexplained variation as shown in Figures 3, 4, and 5.

Høgetveit and Barton (1976) state that they consider urine Ni concentrations an undesirable monitoring method since only 24-hr. collection totals are indicative of atmospheric nickel concentrations. The authors point out that 24-hr. collections require cooperation by workers and avoiding contamination during sample collection at work.

Some investigators present both types of sets of values, but not all did, in fact, collect 24-hour urines. In addition, the calculation of nickel concentration relative to creatinine to control for renal function is not employed or reported by most investigators.

Finally, the number of subjects in most studies is quite small, and the effects of sex and age cannot be evaluated. Equally, there are no data to assess the association between race, urban-rural residential status, geographical

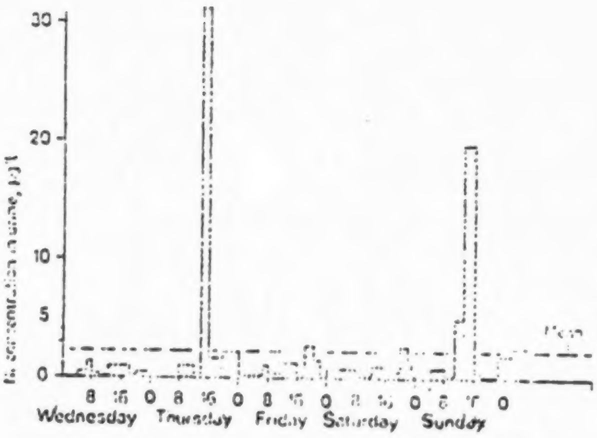

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Figure 3. Urine Ni concentrations in consecutive determinations of urinary nickel from a healthy, nonallergic volunteer. Mean Ni content: 2.2 µg Ni/l urine. From Spruit and Bongaarts (1977a).

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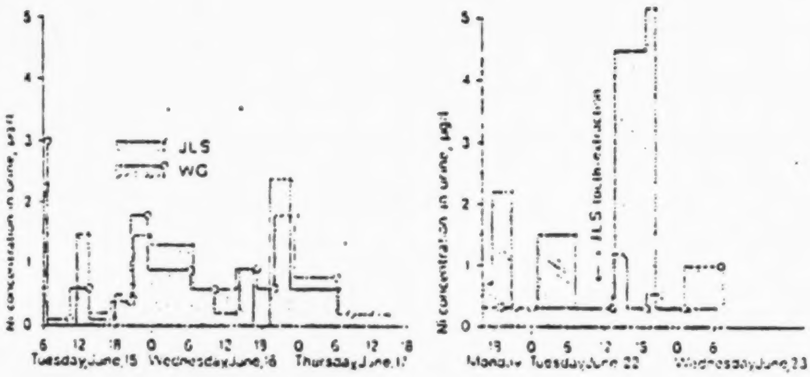

Figure 4. Urine Ni concentration of two nonallergic patients showing influence of toothache and extraction. From Spruit and Bongaarts (1977a).

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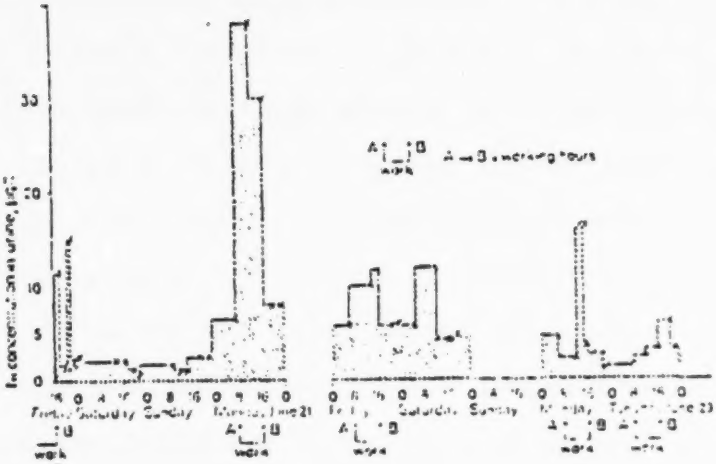

Figure 5. Urine Ni concentration in an occupationally exposed, nonallergic volunteer. Mean value 6.0 µg Ni/l urine and peak values up to 40 µg/l urine during working hours. From Spruit and Bongaarts (1977a).

location, degree of industrialization, and urine Ni levels, so that these variables cannot be examined. There are no data for children and effect of the age gradient cannot be determined for urine concentrations.

The values presented in Table 9 show six findings of remarkable agreement ranging from 0.20 to 0.27 μg/dl for mean values. There is no obvious explanation for the other disparate values found, although analytical problems may have played a part.

Bernacki et al. (1978) determined urine concentrations by volume and creatinine ratio for workers with different environmental exposures. Table 10 shows the findings for exposed, nonexposed, and control subjects as well as air concentrations for seven work environments. There is only partial concordance between atmospheric concentrations and urine values. In view of Høgetveit's findings of the role of different nickel compounds in elevation of plasma levels, it seems that total nickel concentrations in air are not the most useful indicator of variation in exposure effects, and that concentrations of specific compounds might be required to explain associations.

Høgetveit and Barton (1976) found an average urine nickel concentration of 8.9 μg/dl for 729 samples from 305 workers, while the value for controls was 2.1 μg/dl. The data for average urine concentrations for different work sites and exposure to different nickel compounds are not given.

Figure 6 shows the effect of occupational exposure over a 40-day period for both plasma and urine concentrations in two temporary employees, while Figure 7 shows the data for a control subject over a period of 4.5 months. The values showed variation between individual determinations but the range remains below occupational exposure levels.

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TABLE 9. NICKEL CONCENTRATIONS IN HUMAN URINE

| Authors | Method | Area | No. of subjects | Nickel concentration, μg/dl (μg/day) Mean | Nickel concentration, μg/dl (μg/day) Range |
|---|---|---|---|---|---|
| Sunderman (1965) | Atomic absorption | Pennsylvania | 17 | 1.8 (19.8) | 0.4-3.1 |
| Nomoto and Sunderman (1970) | Atomic absorption | Connecticut | 26 | 0.23 (2.4) | 0.10-0.52 (1.0-5.6) |
| Lehnert et al. (1970) | Atomic absorption | Germany | 15 | (9.3) | (5.7-12.7) |
| McNeely et al. (1972) | Atomic absorption | Connecticut | 20 | 0.20 (2.5) | 0.07-0.40 (0.05-6.0) |
| Høgetveit (1976) | Atomic absorption | Norway | a | 2.1 | 0.3-4.2 |
| Spruit (1977) | Atomic absorption | Netherlands | 10 | 0.06 | a |
| Mikac-Devíc et al. (1977) | Atomic absorption | Connecticut | a | 0.27 | a |
| Bernacki et al. (1978) | Atomic absorption | Connecticut | 19 | 0.27[b] | 0.04-0.51[b] |
| Ader and Stoeppler (1978) | Atomic Absorption | a | a | 0.2 | a |

[a] Not specified.

[b] Ni:2.5 ± 1.3 μg/g creatine (range 0.7-5.7 μg/g creatine); all samples with specific gravity < 1.012 discarded.

TABLE 10. NICKEL CONCENTRATIONS IN URINE SPECIMENS FROM WORKERS IN TWELVE OCCUPATIONAL GROUPS[a]

| Group | Occupation | No. of subjects and sex | Description | Atmospheric Ni conc, μg/m$^3$ [b] | Urine μg/l. | Concn[b] μg/g creatinine |
|---|---|---|---|---|---|---|
| A | Hospital workers | 19 (15M,4F) | Physicians, technologists, and clerks | Not measured | 2.7±1.6<br>(0.4-5.1) | 2.5±1.3<br>(0.7-5.7) |
| B | Nonexposed industrial workers | 23 (20M,3F) | Managers, office workers and storekeepers | Not measured | 3.2±2.6<br>(0.3-8.5) | 2.7±1.7<br>(0.6-6.1) |
| C | Coal gasification workers | 9M | Ni-catalyzed hydrogenation process workers | Not measured | 4.2±2.4<br>(0.4-7.9) | 3.2±1.6<br>(0.1-5.8) |
| D | Buffers/polishers | 7 (6M,1F) | Abrasive buffing, polishing and deburring aircraft parts made of Ni-alloys | 26±48<br>(0.05-129) | 4.1±3.2<br>(0.5-9.5) | 2.4±1.4<br>(0.5-4.7) |
| E | External grinders | 9 (7M,2F) | Abrasive wheel grinding of exteriors of parts made of Ni alloys | 1.6±3.0<br>(2.1-8.8) | 5.4±2.4<br>(2.1-8.8) | 3.5±1.6<br>(1.7-6.1) |
| F | Arc welders | 10 (7M,3F) | DC arc welding of aircraft parts made of Ni alloys | 6.0±14.3<br>(0.2-46) | 6.3±4.1[c]<br>(1.6-14) | 5.6±6.2<br>(1.1-17) |
| G | Bench mechanics | 8 (4M,4F) | Assembling, fitting, and finishing parts made of Ni alloys | 52±94<br>(0.01±252) | 12.2±13.6[c]<br>(1.4-41) | 7.2±6.8[c]<br>(0.7-20) |
| H | Nickel battery workers | 6 (5M,1F) | Fabricating Ni-Cd or Ni-Zn electrical storage batteries | Not measured | 11.7±7.75[d]<br>(3.4-25) | 10.2±6.4[d]<br>(7.2-23) |
| I | Metal sprayers | 5 (4M,1F) | Flame spraying Ni-containing powders in plasma phase onto aircraft parts | 2.4±2.6<br>(0.04-6.5) | 17.2±9.8[d]<br>(1.4-26) | 16.0±21.9<br>(1.4-54) |
| J | Electroplaters | 11M | Intermittent exposure to Ni in combined electrodeposition operations involving Ag, Cd, Cr, or Cr plating as well as Ni | 0.8±0.9<br>(0.04-2.1) | 10.5±8.1[d]<br>(1.3-30) | 5.9±5.0[c]<br>(1.0-20) |
| K | Nickel platers | 21M | Full-time work in Ni plating operations | Not measured | 27.5±21.2[e]<br>(3.6-65) | 19.0±14.7[e]<br>(2.4-47) |
| L | Nickel refinery workers | 15M | Workers in a nickel refinery that employs the electrolytic process | 489±560<br>(20-2,200) | 222±226[e]<br>(8.6-8.3) | 124±109[e]<br>(6.1-287) |

[a] From Bernacki et al. (1978).

[b] Mean ± SD with range in parentheses.

[c] $p < 0.05$ vs control subjects in Group A, computed by t test.

[d] $p < 0.01$ vs control subjects in Group A, computed by t test

[e] $p < 0.001$ vs control subjects in Group A, computed by t tes

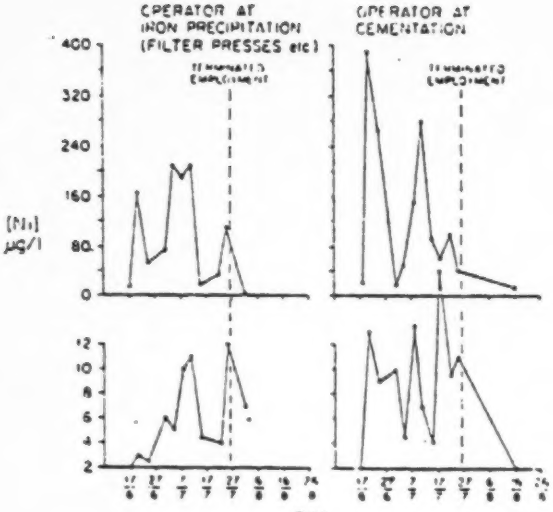

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Figure 6. Plasma and urine nickel values in two temporary workers tested every 10 days. From Høgetveit and Barton (1976).

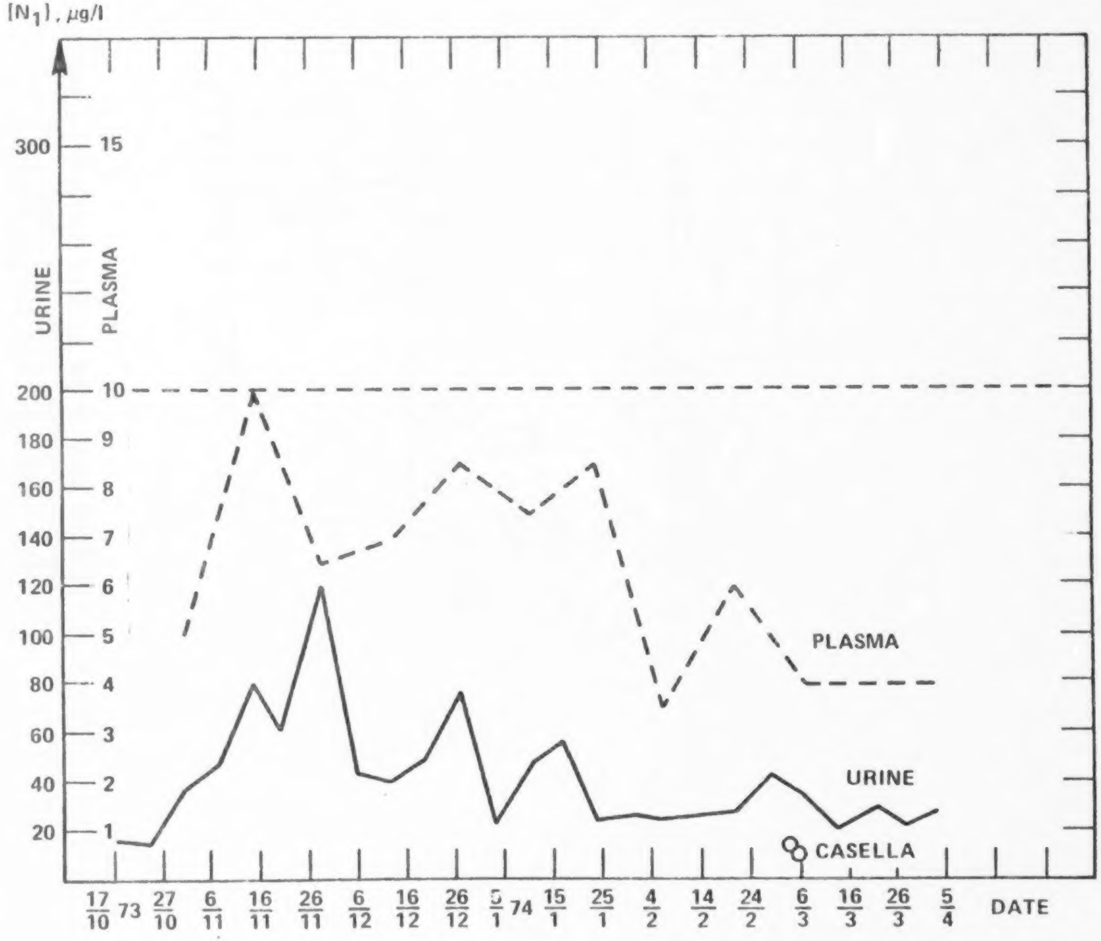

Figure 7. Plasma and urine nickel concentrations in a student volunteer. From Høgeveit and Barton (1976).

Spruit and Bongaarts (1977a) found a mean nickel urine concentration of 1.8 μg/dl for seven occupationally exposed individuals and 0.06 μg/dl for 10 unexposed males. After a two-week vacation period, the mean value for the exposed workers had gone down to 0.18 μg/dl.

The same authors report on the urine and plasma concentrations in a healthy, nonexposed volunteer after ingestion of 5 mg of nickel as a solution of nickel sulfate. Figure 8 shows these concentrations during the first 8 days after ingestion. Plasma and urine concentrations do not follow the same pattern of response.

As in the case of plasma and serum concentrations, studies of urine concentrations in occupationally exposed persons have not reported smoking status or age. The effect of smoking, consequently, cannot be examined at this time. Age as a variable in nickel urine concentrations cannot be assessed at this time, since there are no available data. It should be pointed out that Høgetveit and Barton's data (1976) showing employment cohorts cannot serve as a surrogate variable for age cohorts. Kreyberg's (1978) analysis of lung cancer in workers from that nickel refinery found that post-World War II employees were considerably older at the start of their employment than the prewar groups and that age cannot be assumed from employment cohort membership.

The use of hair in assessing toxic metal exposure has several appealing features: hair sampling represents a rapid, noninvasive means of assessing internal exposure and involves a matrix which can be stored indefinitely in sealed containers. Also, segmental analyses along the length of the hair

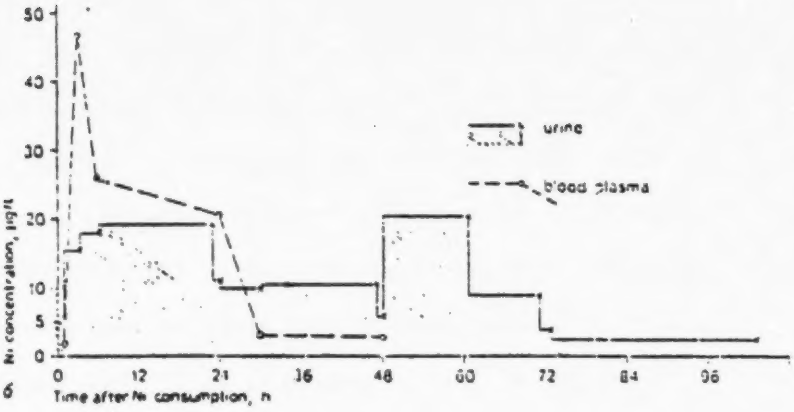

Figure 8. Blood plasma and Urinary Ni content of a healthy, non-allergic volunteer after oral consumption of 5 mg Ni (solution of nickel sulfate at time 0. Mean of 11 urine determinations during the first 48 hrs. 10.9 µg Ni/l urine; mean of 8 plasma determinations during the first 48 hrs. 13.5 µg Ni/l plasma.
From Spruit and Bongaarts (1977a).

samples should provide some sort of chronological index of chronic and episodic acute exposure to an agent.

One of the most vexing problems associated with determination of hair nickel levels is that of external contamination, not only from airborne and water-borne nickel but also from the use of hair preparations which may contain appreciable amounts of nickel. Thus, the relative effectiveness of chemical debridement methods will markedly influence the resulting nickel levels. Cleaning techniques which not only remove surface nickel but penetrate the matrix of the hair may yield values that are too low. Conversely, ineffective cleaning will yield nickel levels from both internal and external exposure. A second problem is the sampling from different places along the hair shaft by different laboratories.

It would appear that standardization of cleaning and sampling techniques is urgently required before hair nickel levels from various laboratories can be compared and conclusions made regarding the exposure - hair level relationship.

Table 11 shows hair nickel values from studies employing atomic absorption spectrometry techniques. Samples for the Schroeder study were of unspecified length and were collected from a barbershop. Nechay's samples consisted of hair obtained 5 cm from the scalp. The Eads study obtained samples from barbershops and beauty shops but the location and length of the hair fibers are not specified. Spruit reports taking hair samples at about 1 cm from the scalp.

In the Schroeder study, the hair was washed in tetrachloride. Eads reports elimination of "obviously bleached and dyed hair," 48-hour soaking and several rinses in deionized water, 1-hour soak, repeated rinses in methanol,

TABLE 11. NICKEL CONCENTRATIONS IN HUMAN HAIR

| Authors | Method | Area | No. and sex of subjects | Nickel concentration, ppm | |
|---|---|---|---|---|---|
| | | | | Mean | Range |
| Schroeder and Nason (1969 | Atomic absorption | New Hampshire | 79M<br>25F | 0.97<br>3.69 | |
| Eads and Lambdin (1973) | Atomic absorption | Texas | 19M<br>21F | 1.9<br>3.4 | 0.9-7.2<br>0.7-7.5 |
| Nechay (1973) | Atomic absorption | Connecticut | 20M | 0.22 | 0.13-0.51 |
| Spruit (1977) | Atomic absorption | Netherlands | 10M<br>14F | 0.6<br>1.0 | |

and drying in a draft oven at 110°C. Nechay states that hair was washed in nonionic detergent, and Spruit gives no information on washing procedures.

All authors except Nechay and Sunderman report significant differences in values for men and women. In view of the differences in sample collection, washing techniques, and details of analytic procedures, it is impossible to reach conclusions about the nickel content of hair from adults without occupational exposure.

Chattopradhyay and Jervis (1974) reported hair nickel values for 76 rural subjects, 45 urban subjects, and 121 subjects from urban regions near refineries. The hair samples were taken by clipping "close to the head," and the samples were washed sequentially with ether, alcohol, and distilled water, and then analyzed by nuclear activation techniques. Precision and accuracy for nickel determination as evaluated by the National Bureau of Standards and Environmental Protection Agency - NBS standard materials analyses were good: the value for orchard leaves was 1.27 ± 0.08 ppm compared to the NBS value of 1.3 ± 0.2 ppm and the value for fly ash was 96.8 ± 3.2 compared to the EPA-NBS concentration of 98 ± 3 ppm. The median and range for the rural subjects were 2.1 (1.6 to 17) ppm; for the urban subjects 2.4 (1.2 to 20) ppm; and 3.6 (1.1 to 32) ppm for the subjects from urban regions near refineries.

Creason et al. (1975) investigated hair nickel concentrations in adults and children in communities within the New York metropolitan area. The communities had different levels of nickel in the environment as measured in dustfall, home dust, and soil. The hair samples were contributed by the subjects as they obtained a "normal hair cut or trim" Dry ashing and emission spectroscopy were used as the analytic method. Hair was washed in a detergent solution. Nickel concentrations observed showed no significant differences for children (0 to 15 years old) and adults ≥ 16 years old. The concentrations were: for 265 children, a geometric mean of 0.51, ± 0.20 to 1.30 geometric SD, range of 0.036 to 11.0 ppm; for 194 adults, the results were 0.74 geometric mean, ± 0.27=2.07 geometric SD, range 0.045 to 11.0 ppm. For nickel, environmental exposure gradients were significantly associated for children but not for adults.

The role of hair as an excretion tissue for nickel is complicated by the findings for nickel concentrations in scalp hair and pubic hair of women studied for maternal-fetal levels of trace elements. Creason et al. (1976) used dry ashing and emission spectroscopy as the method for nickel concentration assessment. The mean for 63 samples of scalp hair was 1.7 μg/g and the geometric mean 1.0 μg/g , while 110 samples of pubic hair showed 0.7 and 0.4 μg/g , respectively. The differences in these values are not explained, and the question of the relative role of scalp hair as an indicator of secretion in relation to exposure and body burden remains unanswered.

The excretion of trace metals such as nickel via hair has been demonstrated in the above studies. However, the data available for nickel concentrations in various "normal" populations are too sparse to permit one to reach conclusions. Most investigators have found significant differences between male and female hair nickel concentrations (Table 11).

Spruit and Bongaarts (1977b) reported the mean hair nickel concentration for eight occupationally exposed men as 14.5 ppm. The value for nonexposed males was reported as 0.6 ppm.

Hair nickel determinations are not usually carried out with industrial population assessment and such studies appear to restrict themselves to evaluation of blood and urine nickel levels, since these are more reflective of current exposure.

Crucial to the assessment of the effects of nickel on human populations is the necessity of determining key tissue levels of the element and, where possible, total body burden. It is generally not feasible to assess these levels in humans other than through autopsy studies, and several investigators have carried out such surveys of nickel levels in selected organs. These studies can be roughly classed into case studies concerned with specific diseases or population studies, as discussed below. No in vivo studies for nickel have been reported, though Harvey et al. (1975) performed such a study using neutron-activation analysis for cadmium.

It is necessary to point out some limitations of the data obtained from autopsy studies. The cases coming to autopsy do not really constitute a representative sample of a given population. The requirements for performing an autopsy vary from country to country, and different population segments differ significantly in their willingness to consent to autopsies not legally required. It is also well known that this attitude is related to social status, occupation, and housing, all of which are factors associated with different degrees of exposures to pollutants as well as with nutritional and health status. The technical problems of speed, collection of information retrospectively, and the proportion of dead without living contacts all add to the difficulty of obtaining reliable data needed to analyze and interpret findings. Finally, there is the problem of defining "normal" or "healthy" individuals. Usually, accidental death victims are defined as "normal" or "healthy" subjects, and the quality of the examination of accident cases to determine this status may also vary. In the case of investigations of nickel in tissue from cadavers, there is the problem of the effect of pathology, stress, or trauma, all of which can change nickel levels.

There are very few data in the literature concerning nickel tissue levels and total body burden. The NAS report (1975) summarized the findings from the work by Tipton and her group and concluded that the total nickel content in a normal man is approximately 10 mg. Table 12 is derived from the NAS report presenting Schroeder's findings.

Bernstein et al. (1974) reported results for 25 autopsies of subjects aged 20 to 40 years from New York City, with a diagnosis of sudden death and no indication of illness. Tissues taken from the right lung and paratracheal, peribronchial, and hilar lymph nodes were ashed in nitric acid and analyzed with atomic absorption spectrometry. Mean values were 0.23 ± 0.06 μg Ni/g wet weight for lung tissue and 0.81 ± 0.41 μg net weight for lymph nodes. Numeric values for concentrations found in liver, kidney, blood, and bone (three vertebrae) were not reported, and Figure 9 shows means and standard deviations.

Sumino et al. (1975) reported on heavy metals in tissues from autopsies of 30 persons who lived in the same prefecture in Japan. The causes of death were trauma, suffocation, overdoses of sleeping pills, and carbon monoxide intoxication. Ages ranged from 10 to > 60 for the 15 males and 10 to > 60 for the 15 females. Twenty different types of tissue were removed but not all types from each subject so that the number of samples for different tissues vary. Nickel concentrations for those tissue samples with detectable amounts were reported. The analytic method of nickel was dry ashing, residue digestion, and flame atomic absorption spectroscopy. The detection level was not stated,

TABLE 12. NICKEL CONCENTRATIONS IN KIDNEY AND LIVER, BY GEOGRAPHIC REGION[a]

| Region | Kidney |  |  | Liver |  |  |
|---|---|---|---|---|---|---|
|  | No. of samples | Mean nickel concentration, ppm of ash | Frequency of nickel occurrence, % | No. of samples | Mean nickel concentration, ppm of ash | Frequency of nickel occurrence, % |
| United States | 161 | 7 | 27 | 163 | 6 | 22 |
| Alaska | 2 | 35 | 100 | 1 | 36 | 100 |
| Honolulu | 5 | 4 | 40 | 5 | 4 | 40 |
| Non-U.S. subjects | 146 | 12.4 | 58.2 | 141 | 11.0 | 44.0 |

[a] From Nat. Acad. Sci. (1975).

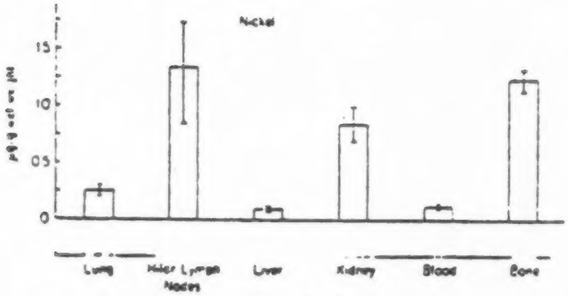

Figure 9. Distribution of nickel in human tissues. From Bernstein (1974).

but the report of the nickel concentrations in the different tissues indicates that not all samples showed detectable amounts of nickel. Table 13 shows some of the nickel concentrations. The total body burden for nickel was calculated as $\geq$ 5.7 mg of nickel for a body weight of 55 kg.

The NAS report (1975) contains Sunderman's data (1971) obtained by an atomic absorption method from material from four autopsies (Table 14).

Nickel concentrations in lung tissue for 15 control subjects in a study of bituminous coal miners were reported by Sweet (1974). Emission spectroscopy was employed for nickel analysis. The mean nickel concentration was 0.6 µg/g dry weight.

Creason (1976) reported maternal and fetal tissue levels of nickel. Dry ashing and emission spectroscopy analysis was employed for nickel determinations. Placental tissue from 160 women yielded an arithmetic mean of 3.4 and a geometric mean of 2.2 µg/100 g with 10 percent of the samples giving values below the detection limit of the method employed.

The data available for nickel concentrations in normal human tissue are very limited and analytic procedures differ. At this time, it seems unwise to draw conclusions as to concentrations within various organs or total body burden in normal populations. An age gradient does not seem likely, but adequate data are not available to assess that aspect either.

Indraprasit et al. (1974) reported nickel concentrations in tissues obtained from 220 random autopsies. On the basis of clinical findings the patient population was divided into three groups. The first group was classified as "controls" (based on serum creatinine < 1.5 mg percent) and consisted of 116 patients. The other groups, consisting of 104 patients, were

## TABLE 13. NICKEL CONCENTRATIONS IN JAPANESE HUMAN TISSUES[a]

| Organ | No. of cases | Nickel concentration, μg/g wet weight<br>Mean + SD | Median | Range |
|---|---|---|---|---|
| Lung | 30 | 0.16 ± 0.094 | 0.16 | 0.038-0.44 |
| Liver | 27 | 0.078 ± 0.046 | 0.068 | 0.028-0.22 |
| Kidney | 28 | 0.098 ± 0.070 | 0.081 | 0.012-0.30 |

TABLE 14. NICKEL CONCENTRATION IN HUMAN TISSUES[a]

| Subject no. | Sex | Age, years | Cause of death | Nickel concentration, μg/100g |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Wet Weight |  |  | Dry Weight |  |  |
|  |  |  |  | Lung | Liver | Heart | Lung | Liver | Heart |
| 1 | M | 44 | Stab wounds | 2.40 | 0.52 | 0.62 | 14.6 | 2.1 | 2.3 |
| 2 | F | 40 | Barbiturate poisoning | 2.20 | 0.86 | 0.57 | 12.1 | 3.2 | 2.4 |
| 3 | M | 18 | Hanging | 0.81 | 0.76 | 0.43 | 3.3 | 2.6 | 1.6 |
| 4 | F | 22 | Carbon monoxide poisoning | 0.96 | 1.32 | 0.83 | 4.3 | 4.8 | 3.0 |
|  | Mean |  |  | 1.59 | 0.87 | 0.61 | 8.6 | 3.2 | 2.3 |

[a] Derived from Sunderman et al. (1971).

equally divided into those with acute renal failure and those with chronic renal failure at time of death. Freeze-dried tissue samples were analyzed by emission spectroscopy. The limit of detection for nickel was 0.5 ppm. Renal cortex tissue was obtained for all 220 subjects, but liver and spleen tissue was collected for only the last 144 subjects. The 220 cases were obtained by random sampling of cadavers during 1 calendar year. Table 15 shows the results of the analysis for the three organs for the three groups. The authors state that the limit of detection and the consequent low percentages of tissues with detectable limits preclude any significant findings of relationships between renal failure and nickel concentrations, but it seems worthy of note that there is a consistent gradient of detectability for the three disease categories, i.e., levels of nickel rising to detectability.

There is little in the literature reporting autopsy tissue studies of nickel refinery workers, except from cases of fatal nickel carbonyl poisoning (Natl. Acad. Sci., 1975), where highest levels of nickel are seen in lung, with lesser amounts in kidneys, liver, and brain. In a study of coal workers' penumoconiosis (CWP), nickel content of lung tissue of bituminous coal miners with CWP showed significantly higher nickel concentrations in lung tissue when compared to values obtained for nonoccupationally exposed males and females residing in the area (Sweet et al., 1974). The nickel concentrations for coal miners with CWP ranged from 5.0 μg/g dry weight to 0.5 μg/g for six groups of disease severity. The mean for the entire group was 2.5 μg/g dry weight and the mean value for controls was 0.6 μg/g .

TABLE 15. NICKEL CONCENTRATIONS IN RENAL CORTEX, LIVER, AND SPLEEN FOR NORMALS AND PATIENTS WITH ACUTE OR CHRONIC RENAL FAILURE

| | Kidney | | Liver | | Spleen | |
|---|---|---|---|---|---|---|
| | Percent detectability | Mean Ni, ppm dry wt | Percent detectability | Mean Ni, ppm dry wt | Percent detectability | Mean Ni, ppm dry wt |
| Normal[b] | 27 | 1.82 | 16 | 1.85 | 16 | 1.72 |
| ARF[c] | 39 | 1.86 | 39 | 2.14 | 38 | 2.11 |
| CRF[d] | 34 | 1.82 | 43 | 1.95 | 40 | 1.97 |

[a] From Indraprasit et al. (1974).

[b] Normal: no acute or chronic renal failure present at time of death.

[c] ARF: acute renal failure present at time of death.

[d] CRF: chronic renal failure present at time of death.

## Metabolism

A number of disease states and other physiological stresses are reported to alter the movement and tissue distribution of nickel in man as well as experimental animals. Furthermore, in vivo movement of nickel may be deliberately altered to enhance nickel removal from the organism to minimize toxicity in cases of excessive exposure, specifically via the use of nickel chelating agents in the clinical management of nickel poisoning.

In man, increased levels of serum nickel are seen in cases of acute myocardial infarction (D'Alonzo and Pell, 1963; Sunderman et al., 1972a; McNeely et al., 1971), such alterations presently being considered as secondary to leukocytosis and leukocytolysis (Sunderman, 1977).

Serum nickel levels are also elevated in acute stroke and extensive burn injury (McNeely et al., 1971), while reduction is seen in hepatic cirrhosis or uremia, possibly secondary to hypoalbuminemia.

Palo and Savolainen (1973) report that hepatic nickel was increased 10-fold over normal values in a deceased patient with aspartylglycosaminuria, a metabolic disorder characterized by reduced activity of aspartyl-β-glucosaminidase.

Other stresses appear to have an effect on nickel metabolism. Significant reduction in serum nickel has been seen in mill workers exposed to extremes of heat (Szadkowski et al., 1970), probably due to excessive nickel loss through sweating, as was noted earlier. While tissue nickel levels are reported to be elevated in rats during pregnancy (Spoerl and Kirchgessner, 1977), no comparable data are available for man.

The use of various classes of chelating agents to expedite the removal of nickel from man and animals has been reported with the goal of developing efficient chemotherapeutic agents for use in nickel poisoning. The data have been reviewed (Natl. Acad. Sci., 1975; Sunderman, 1977) and will only be summarized in this section.

On the basis of reported clinical experience, sodium diethyldithiocarbamate (dithiocarb) is presently the drug of choice in the management of nickel carbonyl poisoning, being preferable overall to EDTA salts, 2, 3-dimercapto-propanol (BAL), and penicillamine. In all cases, the agents work to accelerate the urinary excretion of absorbed amounts of nickel before extensive tissue injury can result.

There is a growing body of literature that establishes an essential role for nickel, at least in experimental animals, and the earlier studies have been reviewed (Natl. Acad. Sci., 1975; Neilsen and Sandstead, 1974; Nielsen, 1976; Spears and Hatfield, 1977; Sunderman, 1977).

Mertz (1970) has spelled out criteria for essentiality of trace elements as micronutrients, and this discussion will focus primarily on one of the most critical of these: demonstration of specific deficiency-related syndromes which are prevented or cured by the element alone.

Earlier workers in trace-element nutritional research coulc not demonstrate any consistent effects of nickel deficiency (Natl. Acad. Sci., 1975; Spears and Hatfield, 1977) owing in part to the technical difficulties of controlling nickel intake because of its ubiquity. Later workers have demonstrated adverse effects of nickel deprivation in various animal models.

Nielsen and Higgs (1971) have shown a nickel-deficiency syndrome in chicks fed nickel at levels of 40 to 80 ppb (control diet: 3 to 5 ppm) characterized by swollen hock joints, scaly dermatitis of the legs, and fat-depleted livers. Sunderman et al. (1972b) observed ultrastructural lesions such as perimitochondrial dilation of rough endoplasmic reticulum in hepatocytes of chicks fed a diet having 44 ppb nickel. Nielsen and Ollerich (1974) also noted hepatic abnormalities similar to those reported by Sunderman et al. (1972b). Nickel is also essential in swine nutrition, pigs fed a diet having 100 ppb decreased growth rate, impaired reproduction, and a rough hair coat (Anke et al., 1973).

Growth responses to nickel supplementation have also been reported for rats (Nielsen et al., 1975; Schnegg and Kirchgessner, 1975a; Schroeder et al., 1974). Rats maintained on nickel-deficient diets through three successive generations showed a 16 percent weight loss in the first and 26 percent weight loss in the second generation compared to nickel-supplemented controls (Schnegg and Kirchgessner, 1975).

Effects on reproduction have been documented in rats (Nielsen et al., 1975) and swine (Anke et al., 1974; Schnegg and Kirchgessner, 1975a), mainly in terms of increased mortality during the suckling period in rats and smaller litter size.

Nickel appears to be essential also for ruminant nutrition (Spears and Hatfield, 1977). Spears and Hatfield (1977) demonstrated disturbances in metabolic parameters in lambs maintained on a low-nickel diet (65 ppb), indosing intraperitoneally yields lung carcinomas in mice (Stoner et al., 1976) when nickel acetate is used, while nickelocene, an organonickel "sandwich" structure, induces sarcomas in rats and hamsters when given intramuscularly (Haro et al., 1968; Furst and Schlauder, 1971).

Schnegg and Kirchgessner (1975b; 1976) demonstrated that nickel deficiency leads to reduced iron contents in organs and iron deficiency anemia, resulting from markedly impaired iron absorption.

Nickel appears to pertain also to other criteria for essentiality (Mertz, 1970): apparent homeostatic control and partial transport by specific nickel-carrier proteins (see Metabolism section). Fishbein et al. (1976), furthermore, have reported that jackbean urease is a natural nickel metalloenzyme, and it is also possible that rumen bacterial urease may also have a specific nickel requirement (Spears et al., 1977).

## Excretion

The excretory routes for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake.

Unabsorbed dietary nickel is simply lost in the feces. Given the relatively low extent of gastrointestinal absorption (vide supra), fecal levels of nickel roughly approximate daily dietary intake, 300-500 µg/day in man.

Urinary excretion in man and animals is usually the major clearance route for absorbed nickel. Normal levels in urine vary considerably in the literature, and earlier value variance probably reflects methodological limitations. More recent studies suggest values of 2-4 µg/l. (McNeely et al., 1972; Anderson et al., 1978).

While biliary excretion is known to occur in the rat (Smith and Hackley, 1968), the calf (O'Dell et al., 1971), and the rabbit (Onkelinx et al., 1973), its role in nickel metabolism in man is unknown.

Sweat can constitute a major route of nickel excretion. Hohnadel and co-workers (1973) determined nickel levels in the sweat of healthy subjects sauna bathing for brief periods at 93°C to be 52 ± 36 µg/l for men and 131 ± 65 µg/l for women.

The role of nickel deposition in hair as an excretory mechanism in man has prompted a number of studies. The use of hair nickel levels in assessing overall nickel body burdens as well as exposure chronology remains to be widely accepted. Its utility in epidemiological studies is discussed elsewhere. Schroeder and Nason (1969) have reported sex-related differences in nickel levels of human hair samples, female subjects having nickel levels (3.96 µg/g, S.E.M. = ± 1.06) about fourfold those of men (0.97 µg/g, S.E.M. = ± 0.15). Such a difference, however, was not encountered by Nechay and Sunderman (1973) nor were their average sample values as high. The differences in these two studies serve to point out some of the difficulties in establishing quantitative relationships for the role of hair levels in nickel metabolism.

In experimental animals, urinary excretion is the main clearance route for nickel compounds introduced parenterally.

Animals exposed to nickel carbonyl by inhalation exhale a part of the respiratory burden of this agent within 2 to 4 hours while the balance is slowly degraded in vivo to divalent nickel and carbon monoxide, with nickel eventually undergoing urinary excretion (Sunderman and Selin, 1968; Mikheyev, 1971).

## EFFECTS

### Acute, Subacute, and Chronic Toxicity

The purpose of this section of the document is to discuss those biological and adverse health effects which have been documented for nickel in man and animals. It is not the purpose of this treatment to assemble a thorough review of the literature on nickel, but rather to focus on those reported effects which have more direct relevance for ultimate evaluation of health risks in man as posed by nickel in its various forms and under varying exposure conditions.

Comparatively speaking, the major concern with nickel on human health effects has centered on nickel carcinogenesis and nickel's allergenic properties; thus, for emphasis, these two areas are discussed separately from the systemic toxicity of nickel.

Unlike the case with toxic elements such as cadmium, lead, and mercury, there appears to be an increasingly strong case for nickel being an essential element, at least in animals, as well as a toxicant. Thus, the ultimate use of exposure regulation and health benefit/health cost balance is made more complicated, in that desirable nickel intake must lie somewhere between amounts adequate to serve essentiality and not enough to precipitate adverse effects. The data pertinent to nickel's role as a probable essential element are discussed in the final segment of this chapter.

Since the systemic toxicity of an agent is a macroscopic reflection of the deleterious interactions of the substance at the molecular, organellar, and cellular level, it is helpful to discuss those studies that characterize effects at these levels of functional and structural organization. This approach of course is an arbitrary, if widely used, device to elaborate the range and types of toxicant effects. In reality, the overall response of an organism to a toxic agent is a complex integration of discretely determined phenomena. In some cases, it is more appropriate to discuss subcellular and cellular effects with the associated systemic effects and hence, the cellular level is not covered here.

The toxicity of nickel to man and animals is a function of the chemical form of the element and the route of exposure.

With regard to oral intake, nickel metal is comparatively nontoxic, dogs and cats being able to tolerate up to 12 mg Ni/kg daily for up to 200 days without ill effects (Stokinger, 1963). Nickel carbonate, nickel soaps, or nickel catalysts given to young rats at levels up to 1000 ppm in diet for 8 weeks had no effect on growth rate (Phatak and Patwardhan, 1952); similarly, these forms of nickel at 1000 ppm when fed to monkeys for up to 6 months did not affect growth, behavior, or hematological indices (Phatak and Patwardan, 1952).

The gross toxicity of a number of inorganic and organometallic complexes of nickel in terms of dose versus lethality percentages have been tabulated (Natl. Acad. Sci., 1975).

Exposure to nickel by inhalation or parenteral administration as well as cutaneous contact is of greater significance to the picture of nickel toxicology and the discussion of nickel effects on various systems in man and animals mainly relates to these routes of exposure.

In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl, $NI(CO)_4$, a volatile, colorless liquid formed when finely divided nickel comes into contact with carbon monoxide, as in the Mond

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process for purification of nickel (Mond et al., 1890). The threshold limit value (TLV) for a work day is 1 part per billion (ppb) (Am. Conf. Gov. Ind. Hyg., 1971).

A sizable body of literature has developed over the years dealing with the acute exposure of nickel processing workers to nickel carbonyl by inhalation (Natl. Acad. Sci., 1975; Natl. Inst. Occup. Safety Health, 1977; Sunderman, 1977). Since much of this information is relevant mainly to occupational medicine rather than general environmental health, it is not appropriate to accord it detailed discussion in this document.

According to Sunderman (1970) and Vuopala et al. (1970), who have studied the clinical course of acute nickel carbonyl poisoning in workmen, clinical manifestations include both immediate and delayed symptomology. In the former, frontal headache, vertigo, nausea, vomiting, insomnia, and irritability are commonly seen, followed by an asymptomatic interval before the onset of insidious, more persistent symptoms. These include constrictive chest pains, dry coughing, hyperpnea, cyanosis, occasional gastrointestinal symptoms, sweating, visual disturbances, and severe weakness. Aside from the weakness and hyperpnea, the symptomology strongly resembles that of viral pneumonia.

The lung is the target organ in nickel carbonyl poisoning in man and animals. Pathological pulmonary lesions observed in acute human exposure include pulmonary hemorrhage and edema accompanied by derangement of alveolar cells, degeneration of bronchial epithelium, and formation of fibrinous intra-alveolar exudate. Roentgenological followup on patients surviving the acute episode of exposure frequently indicates pulmonary fibrosis.

The pronounced pulmonary tract lesion formation seen in animals acutely exposed to nickel carbonyl vapor strongly overlaps that reported for cases of acute industrial poisoning, and these have been tabulated in Table 16.

As in man, the lung is the target organ for effects of nickel carbonyl in animals regardless of the route of administration. The response of pulmonary tissue is very rapid, interstitial edema developing within 1 hour of exposure. There is subsequent proliferation and hyperplasia of bronchial epithelium and alveolar lining cells. By several days postexposure, severe intra-alveolar edema with focal hemorrhage and pneumocyte derangement has occurred. Death usually occurs by the fifth day. Animals surviving the acute responses show regression of cytological changes with fibroblastic proliferation within alveolar interstitium.

Adverse effects in animals by inhalation of other forms of nickel have been reported. Bingham et al. (1972) exposed rats to aerosols of both soluble (as the chloride) and insoluble (as the oxide) nickel at levels in the region of those acceptable for human industrial exposure. Hyperplasia of bronchiolar and bronchial epithelium with peribronchial lymphocytic infiltrates was seen. Port et al. (1975) noted that intratracheal injection of a suspension of nickel oxide (5 mg, <5 μm) into Syrian hamsters first treated with influenza A/PR/8 virus 48 hours previously significantly increased mortality versus controls. Surviving animals at this dosing and lesser doses showed mild to severe acute interstitial infiltrate of polymorphonuclear cells and macrophages several weeks later. Additional pathological changes included bronchial epithelial hyperplasia, focal proliferative pleuritis and adenomatosis.

TABLE 16. ACUTE PULMONARY EFFECTS OF NICKEL CARBONYL EXPOSURE IN ANIMALS

| Animal | Dosing | Effects | Reference |
|---|---|---|---|
| Rabbit | Inhalation 1.4 mg/l., 50 min | Intraalveolar hemorrhages, edema and exudate; alveolar cell degeneration by days 1-5 | Armit, 1908 |
| Rat | Inhalation 0.9 mg/l., 30 min | At 2-12 hr, capillary congestion and interstitial edema; at 1-3 hr days, intraalveolar edema; 4-10 days, pulmonary consolidation and interstitial fibrosis | Barnes and Denz, 1951 |
| Rat | Inhalation 0.24 mg/l., 30 min | At 1 hr, pulmonary congestion and edema; at 12 hr-6 days, interstitial pneumonitis with focal atelectosis and peribronchial congestion | Kincaid et al., 1953 |
| Rat, dog | Inhalation 1 mg/l., 30 min | At 1-2 days, intraalveolar edema and swelling of alveolar lining cells; at 3-5 days, inflamation, atelectases and interstitial fibrolytic proliferation | Sunderman et al., 1961 |
| Rat | I.V. 65 mg/kg, single dose | At 1-4 hr, perivascular edema; at 2-5 days, severe pneumonitis with intraalveolar edema, hemorrhage sub-pleural consolidation, hypertrophy and hyperplasia of alveolar lining cells | Hackett and Sundermann, 1967 |
| Rat | I.V. 65 mg/kg, single dose | Ultrastructural alterations, includ ing edema of endothelial cells at 6 hr and massive hypertrophy of membranes and granular pneumocytes at 2-6 days | Hackett and Sundermann, 1969 |

A number of studies have been directed to the effects of nickel on endocrine-mediated physiological processes. As noted in the previous section dealing with nickel metabolism, exposure of animals to nickel especially parenterally consistently shows marked uptake of the element in endocrine tissue: pituitary, adrenals, and pancreas. Thus, disturbances in function might be anticipated.

Various laboratories have cited effects of nickel on aspects of carbohydrate metabolism in different animal species. Bertrand and Mächeboeuf (1926) reported that parenteral exposure of rabbits or dogs to nickel salts antagonized the hypoglycemic action of insulin. Later workers (Kadota and Kurita, 1955; Clary and Vignati, 1973; Freeman and Langslow, 1973; Horak and Sunderman, 1975a,b) observed a rapid, transitory hyperglycemia after parenteral exposure of rabbits, rats, and domestic fowl to nickel (II) salts. In several reports, Horak and Sunderman (1975a,b) noted the effects of nickel (II) on normal, adrenalectomized, and hypophysectomized rats. Injection of nickel chloride (2 or 4 mg/kg) produced prompt elevations in plasma glucose and glucagon levels with a return to normal 2 to 4 hours afterwards, suggesting that hyperglucagonemia may be responsible for the acute hyperglycemic response to divalent nickel (Horak and Sunderman, 1975a). Nickel had the most pronounced hyperglycemic effect when this element was studied versus effects of other ions given in equimolar amounts, while concurrent administration of insulin antagonized the hyperglycemic effect (Horak and Sunderman, 1975b). Kadota and Kurita (1955) observed marked damage to alpha cells and some degranulation and vacuolization of beta cells in the pancreatic islets of Langerhans. Ashrof and Sybers (1974) observed lysis of pancreas exocrine cells in rats fed nickel acetate (0.1 percent).

Human endocrine responses to nickel have been poorly studied, although Tseretili and Mandzhavidze (1969) found pronounced hyperglycemia in workmen accidentally exposed to nickel carbonyl.

Nickel apparently has an effect on the hypothalamic tract in animals, enhancing the release of prolactin-inhibiting factor (PIF) thereby decreasing the release of prolactin from bovine and rat pituitary glands (La Bella et al., 1973a). Furthermore, intravenous administration of small amounts of nickel to urethane-anesthetized, chlorpromazine-treated rats produces signficant depression of serum prolactin without any effect on growth hormone or thyroid-stimulating hormone, although the *in vitro* release of pituitary hormones other than PIF have been demonstrated for bovine and rat pituitary (La Bella et al., 1973b).

Dormer et al. (1973) and Dormer and Ashcroft (1974) have studied the *in vitro* effects of nickel on secretory systems, particularly the release of amylase, insulin, and growth hormone. Nickel (II) was seen to be a potent inhibitor of secretion in all three glands: parotid (amylase), islets of Langerhans (insulin), and pituitary (growth hormone). Inhibition of growth hormone release at nickel levels comparable to those which La Bella et al. (1973b) observed actually to enhance release may reflect differences in tissue handling prior to assay. Dormer et al. (1973) suggested that nickel may block exocytosis by interfering with either secretory-granule migration or membrane fusion and microvilli formation.

Nickel-induced nephropathy in man or animals has not been widely documented. Acute renal injury with proteinuria and hyaline casts were observed by Azary (1879) in cats and dogs given nickel nitrate. Pathological lesions of renal tubules and glomeruli have been seen in rats exposed to nickel carbonyl

(Kincaid et al., 1953; Sunderman et al., 1961; Hackett and Sunderman, 1967). Gitlitz et al. (1975) observed aminoaciduria and proteinuria in rats after single intraperitoneal injection of nickel chloride, the extent of the renal dysfunction being dose-dependent. Proteinuria was observed at a dose of 2 mg/kg, while higher dosing occasioned aminoaciduria. Ultrastructurally, the site of the effect within the kidney appears to be glomerular epithelium. These renal effects were seen to be transitory, abating by the fifth day.

In man, nephrotoxic effects of nickel have been clinically detected in some cases of accidental industrial exposure to nickel carbonyl (Brandes, 1934; Carmichael, 1953). This takes the form of renal edema with hyperemia and parenchymatous degeneration.

Nickel compounds appear to possess low neurotoxic potential save for fatal acute exposures to nickel carbonyl (Natl. Acad. Sci., 1975; Natl. Inst. Occup. Safety Health, 1977).

Neural tissue lesion formation in the latter case is profound, including diffuse punctate hemorrhages in cerebral, cerebellar, and brain stem regions, degeneration of neural fibers, and marked edema.

Intrarenal injection of nickel subsulfide in rats elicits a pronounced erythrocytosis (Jasmin and Riopelle, 1976; Morse et al., 1977; Hopfer and Sunderman, 1978), the erythrogenic effect being apparently unrelated to the carcinogenicity of the compound (Jasmin and Riopelle, 1976). Morse et al. (1977) showed that the erythrocytosis is dose-dependent, is not elicited by intramuscular administration and is associated with marked erythroid hyperplasia of bone marrow. Hopfer and Sunderman (1978) observed a marked inhibition of erythroctyosis when manganese dust was co-administered.

Effects of nickel on thyroid function have been noted by Lestrovoi et al. (1974). Nickel chloride given orally to rats (0.5-5.0 mg/kg/day, 2 to 4 weeks) or by inhalation (0.05 to 0.5 mg/$m^3$) significantly decreased iodine uptake by the thyroid, such an effect being more pronounced for inhaled nickel.

## Allergenic Response

Since allergenic responses to contact with nickel containing compounds has been a major focus of research effort, discussion of this topic is presented as a unified body of information in this section of the document.

Nickel dermatitis and other dermatological effects of nickel have been extensively documented in both nickel worker populations and populations at large (Natl. Acad. Sci., 1975). Originally considered to be a problem in occupational medicine, the more recent clinical and epidemiological picture of nickel sensitivity offers ample proof that it is a widespread problem in individuals not having occupational exposure to nickel but encountering an increasing number of nickel-containing commodities in their everyday environment.

Occupational sources of nickel that have been associated with nickel sensitivity include mining, extraction, and refining of the element as well as such operations as plating, casting, grinding, polishing, and preparation of nickel alloys (Natl. Acad. Sci., 1975). Although the frequency of nickel dermatitis has considerably abated owing to advances in both control technology and industrial medicine, it may still persist in electroplating shops (Natl. Acad. Sci., 1975).

Nonoccupational exposure to nickel leading to dermatitis includes nickel-containing jewelry, coinage, tools, cooking utensils, stainless steel kitchens, prostheses, and clothing fasteners. Women appear to be particularly at risk for dermatitis of the hands, which has been attributed to their continuous contact with many of the nickel-containing commodities noted above (Malten and Spruit, 1969).

Nickel dermatitis in nickel miners, smelters, and refiners and known as "nickel itch" usually begins as itching or burning papular erythema in the web of the fingers and spreading to the fingers, wrists, and forearms. Clinically, the condition is usually manifested as a papular or papulovesicular dermatitis with a tendency toward lichenification, having the characteristics of atopic rather than eczematous dermatitis.

Citing a large number of cases, Calnan (1956), stated that nickel dermatitis has a unique topographical distribution pattern: (1) primary: areas in direct contact with the element; (2) secondary: spreading of the dermatitis in a symmetrical fashion; and (3) associated: afflicted areas having no relation to contact areas. Furthermore, the affliction may persist some time after removal of obvious sources of exposure.

A clear relationship between atopic dermatitis and that elicited by nickel has been confused by conflicting reports in the literature. Watt and Baumann (1968) showed that atopy was present in 15 of 17 young patients with earlobe nickel dermatitis, but other workers (Wilson 1956; Marcussen, 1957; Caron, 1964; Calnan, 1956) have failed to demonstrate any connection between the two disorders. Juhlin et al. (1969) demonstrated elevated immunoglobulin in E (IgE) levels in atopy patients while Wahlberg and Skog (1971) saw no significant increases of IgE in patients having nickel and atopic dermatitis histories.

The occurrence of pustular patch test reactions to nickel sulfate has been considered significant in connecting nickel and atopic dermatitis (Becker and O'Brien, 1959). Uehara et al. (1975) have reported that pustular patch test reactions to 5 percent nickel sulfate were regularly produced in patients with atopic dermatitis, but only when applied to areas of papulae, erythema,

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lichenification, and minimal trauma; such response seldom occurred on normal-appearing skin surface. Furthermore, traumatizing the test areas in control as well as dermatitic subjects furnished positive responses. These workers suggest that pustular patch testing is primarily a primary irritant reaction.

Christensen and Möller (1975a) found that of 66 female patients with hand eczema and nickel allergy, 51 had an eczema of the pompholyx type; i.e., a recurring itching eruption with deeply seated fresh vesicles and little erythema localized on the palms, volar aspects, and sides of fingers. Of these, 41 had pompholyx only, while the remainder had at least one additional diagnosis: allergic contact eczema, irritant dermatitis, nummilar eczema, or atopic dermatitis. These workers also found that the condition was not influenced by any steps taken to minimize external exposure. Subsequently, these investigators (Christensen and Möller (1975b) discovered that oral administration of nickel in 9 of 12 of the earlier subjects aggravated the condition, while intense handling of nickel-containing objects was without effect.

While Kaaber et al. (1978) found little correlation between nickel excretion and the status of dermatitis in their patients, Menne and Thorboe (1976) have reported elevated urinary nickel levels during flare-ups in the dermatitis. De Jongh et al. (1978) found limited correlation between plasma nickel level, urinary excretion of nickel and the clinical activity of the condition in a patient followed during two periods of 5 and 6 weeks each.

Internal exposures to nickel associated with nickel sensitivity and arising from prosthesis alloys have been reviewed (Natl. Acad. Sci., 1975; Samitz and Katz, 1975; Fisher, 1977), and much of these data are summarized in this section.

The most common prosthesis alloys are stainless steel or cobalt-chromium (Vitallum), which may contain nickel in amounts up to 35 percent, generally in the range of 10 to 14 percent (Samitz and Katz, 1975).

Instances of allergic reactions as well as urticarial and eczematous dermatitis have been attributed to implanted prosthesis with resolution of the condition after removal of the devices (Natl. Acad. Sci., 1975; Samitz and Katz, 1975). Apparently, sufficient solubilization of nickel from the surface of the material occurs to trigger an increase in dermal response. In support of this, Samitz and Katz (1975) have shown the release of nickel from stainless steel prosthesis by the action of blood, sweat, and saline.

Fisher (1977), in his review, has counseled caution in interpreting the reports and has recommended specific criteria for proof of nickel dermatitis from a foreign body, to include evidence of surface corrosion and sufficient corrosion to give a positive nickel spot test.

Determination of nickel dermatitis classically involves the use of the patch test and site response to a nickel salt solution or contact with a nickel-containing object. The optimal nickel concentration in patch test solution is set at 2.5 percent (nickel sulfate). Patch test reactions may be ambiguous, in that they can reflect a primary irritation rather than a pre-existing sensitivity (Uehara et al., 1975). Intradermal testing as described by Epstein (1956) has also been employed, but the procedure appears to offer no overall advantage to the conventional method (Natl. Acad. Sci., 1975).

The induction of nickel sensitivity in human subjects has been claimed by Haxthausen (1936) and Burckhardt (1935). In their subjects, prior sensitivity was not ruled out. Furthermore, the concentration of the sensitizing solution, 25 percent, may easily have induced an irritation response. More recently, Vandenberg and Epstein (1963) successfully sensitized 9 percent (16 of 172) of their clinical subjects.

One area of controversy with regard to nickel dermatitis involves the question of hypersensitivity to groups of metals, i.e., cross sensitivity, and various sides of the issue have been reviewed (Natl. Acad. Sci., 1975). Of particular concern is the existence of hypersensitivity to both nickel and cobalt, as the elements occur together in most of the commodities with which susceptible individuals may come in contact.

The underlying mechanisms of nickel sensitivity presumably include (1) diffusion of nickel through the skin, (2) subsequent binding of nickel ion with protein(s) and other skin components, and (3) immunological response to the nickel-macromolecule complex (Natl. Acad. Sci., 1975). In the section on nickel metabolism, the fact that penetration of the outer skin layers by nickel does occur was noted. Jansen et al. (1964) found that nickel in complex with an amino acid (D,L-alaline) was a better sensitizer than nickel alone, while Thulin (1976) observed that inhibition of leukocyte migration in 10 patients with nickel contact dermatitis could be elicited with nickel bound to bovine and human serum albumin or human epidermal protein, but not with nickel ion alone. Hutchinson et al. (1975) noted nickel binding to lymphocyte surfaces from both sensitive and control subjects; thus, nickel binding, per se, is not the key part of the immunological response (lymphocyte transformation).

Useful experimental animal models of nickel sensitivity have only slowly been forthcoming, and only under very specialized conditions.

Nilzen and Wilström (1955) reported the sensitization of guinea pigs to nickel via repeated topical application of nickel sulfate in detergent solution. Samitz and Pomerantz (1958), however, have attributed this to local irritation rather than true allergenic response. Samitz et al. (1975) were unable to induce sensitization in guinea pigs using any nickel compound from complexation of nickel ion with amino acids or guinea pig skin extracts.

Wahlberg (1976) employed intradermal injection of nickel sulfate in highly sensitive guinea pigs. The reactions to the challenge were statistically greater than with control animals. Turk and Parker (1977) reported sensitization to nickel manifested as allergic-type granuloma formation. This required the use of Freund's complete adjuvant followed by weekly intradermal injections of 25 µg of the salt after 2 weeks. Delayed hypersensitivity reactions developed in two of five animals at 5 weeks by use of a split-adjuvant method. Interestingly, these workers also observed (Parker and Turk, 1978) suppression of the delayed hypersensitivity when intratracheal intubation of nickel sulfate was also carried out on these animals.

There are no studies of general populations which relate nickel exposures or levels in tissues and fluids to physiological, subclinical or clinical changes. The studies previously cited do not cover properly designed and executed samples of either total populations or selected population segments which would permit projection of findings to the total population from which subjects were selected. Only occupationally exposed worker populations have been surveyed or monitored in any statistically adequate manner, and these studies will be reported later in connection with nickel carcinogenesis. The literature on adverse health effects in relation to nickel exposure by the general population is limited to the investigation of nickel dermatitis and nickel sensitivity, with only occasional reports related to other diseases or conditions.

## Nickel Sensitivity and Contact Dermatitis

There has not been a single population survey to determine the incidence or prevalence of this allergic condition and its clinical manifestation. The literature is limited to studies of patient populations, and this provides an unreliable basis for projection to the general population. Clinic populations in specialty clinics are self-selected and represent individuals who have decided that their condition is severe enough to require medical care or who have access to medical care and have been referred to specialty clinics. The perception of need for medical care for specific health problems varies significantly by socio-demographic characteristics. For example, a hairdresser or manicurist with dermatitis of the hands will seek medical care, while a factory worker or clerk with the same condition may not do so simply because there are no clients who object. The data presented here, therefore, are of limited value.

The survey conducted by the North American Contact Dermatitis Group (1973) covered 1,200 subjects from 10 cities in the United States. The subjects were selected from outpatient clinics and the private practices of the 13 participating dermatologists. The specific method of selection was not reported, and therefore the proportions of private and clinic patients is not ascertainable from the published report. There are no data on age distribution, but it is probable that all subjects were adults since children are not mentioned. The group used a standardized patch test consisting of 16 allergens and read results in a standardized manner. The nickel allergen was 2.5 percent nickel sulfate. Table 17 shows the results reported as derived from the group's report. The rates of positive reactions are higher for females than for males and the overall reaction rate was 11.2 percent for the 1,200 individuals. The overall rate of reactivity found in data by the International Contact Dermatitis Group (Fregert et al., 1969) was compared with these data. The allergen used in the International group data was 5 percent nickel sulfate, and 4,825 white individuals tested showed a 6.7 percent rate of positive reaction, males showing a reaction rate of 1.8 percent and females 9.9 percent. It is important to point out that both sets of data found nickel sensitivity most frequent in females. The North American study testing 16 allergens found that nine other allergens had higher positive reaction rates than nickel in white males, while the data for the International Contact Dermatitis Group testing 11 allergens found seven allergens with higher positive reaction rates than nickel for the male subjects. Black males in the North American group data showed the highest reaction rate to nickel.

Brun (1974) reported on 1000 cases of contact dermatitis from the University Hospital Clinic in Geneva. Each patient was patch tested with a standard group of 13 allergens including nickel as 3 percent nickel sulfate. The rate of positive reaction to nickel for females was significantly higher than for males. The reaction rates by sex are not reported, but the rate for the total patient group was given as 12.2 percent. Turpentine, with a positive reaction rate of 14.8 percent for the total population exceeded the nickel reaction rate. Hexavalent chrome, the allergen showing the third highest reaction rate, was statistically significantly more frequent in males than females. Comparison with data from the International Contact Dermatitis

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## TABLE 17. NORTH AMERICAN CONTACT DERMATITIS GROUP PATCH TEST RESULTS FOR 2.5 PERCENT NICKEL SULFATE IN 10 CITIES[a]

| Subjects | | Total No. | Positive Reactions | |
|---|---|---|---|---|
| | | | No. | Percent |
| Black | Females | 79 | 14 | 17.7 |
| | Males | 64 | 6 | 9.3 |
| | Total | 143 | 20 | 14.0 |
| White | Females | 612 | 89 | 12.7 |
| | Males | 445 | 22 | 4.4 |
| | Total | 1057 | 111 | 10.5 |
| All | Females | 691 | 103 | 14.9 |
| | Males | 509 | 28 | 5.5 |
| Total | | 1200 | 131 | 11.2 |

[a] From North American Contact Dermatitis Group (1973).

group by specific European cities shows nickel sensitivity is by no means the leading allergen in each location.

The differences in nickel sensitivity rates are not strictly comparable, since the International group tested with 5 percent nickel sulfate solution while the North American group used a 2.5 percent and Brun used a 3 percent nickel sulfate solution.

Spruit and Bongaarts (1977a) investigated the relationship of nickel sensitivity to nickel concentrations in plasma, urine, and hair and found no association. The role of atopy, either personal or familial, in nickel-sensitive and nonsensitive dermatitis cases was examined by Wahlberg (1975). No differences of rates of personal or familial atopy were found for nickel-sensitive and nonsensitive patients with hand eczema. All cases were ladies' hairdressers; they showed a positive reaction rate of 40 percent to nickel sulfate (5 percent) solution.

Both Spruit and Bongaarts (1977b) and Wahlberg (1975) reported that positive reaction to nickel sulfate occurs at very low dilution levels in some individuals. Wahlberg found 5 of 14 positive reactors sensitive to $\leq$ 0.039 percent nickel sulfate solution. Spruit and Bongaarts (1977b) found one female patient with a positive reaction when the solution was 10 μg $Ni^{++}$/1.

Nickel sensitivity is prevalent among women, and nickel content dermatitis occurs frequently not only among women but also among men who are exposed. Nickel is extremely common in the articles and substances found in the home and in metals used for jewelry, metal fasteners of clothing, coinage, etc. Some preparations used in hair dressing contain nickel and consequently hairdressers exhibit nickel dermatitis. The consequences of nickel contact dermatitis seems to vary with the surrounding social factors: male factory workers appear not to be handicapped by it (Spruit and Bongaarts, 1977b) and continue in their work; hairdressers leave their occupation when they develop dermatitis (Wahlberg 1975).

The impact of nickel dermatitis on the health of the total U.S. population cannot be assessed at this time since the prevalence of this condition in the population is unknown. Also, there are no data on the range of severity and the consequences, the costs, of the condition.

## Sensitivity to Nickel in Prostheses

Stainless steel, chrome, and other metal alloys used in prostheses and other surgical devices frequently contain proportions of nickel that have proved to cause reactions in patients ranging from itching to dermatitis to tissue breakdown, requiring replacement of the device. The NAS report (1975) lists the following devices and prostheses reported in the literature as associated with adverse reactions to their nickel contents: wire suture materials; metallic mesh for nasal prostheses; heart valves; intrauterine contraceptive devices; batteries for implanted pacemakers; alloys for dental castings and fillings; and orthopedic implants.

The alloys, contrary to general assumption, appear not to be biologically inert and produce adverse reactions in some of the individuals sensitive to nickel. Two cases of cancer in humans at the site of steel plate implantation were reported. These cancers developed 30 years after implantation in both cases. In both cases the alloys of the plates and screws differed and possibly electrolysis and metallic corrosion may have occurred.

Deutman and colleagues (1977) report on metal sensitivity before and after total hip arthroplasty in 212 cases from their orthopedic service in Groningen, The Netherlands. They instituted their study because recent literature contains reports of reactions to orthopedic implants including loosening of total joint prostheses. The authors studied the pre-operative sensitivity status of 212 patients scheduled for total hip replacement and followed up these patients to ascertain if sensitivity developed after the insertion. Fourteen patients were sensitive to one or more of three metals tested and 11 of these were sensitive to nickel. The allergens used were those recommended by the International Contact Dermatitis Group, that is, for nickel sensitivity, a 2.5 percent nickel sulfate solution was employed in the patch test. (The nickel sulfate solution standard has been changed since the time of the European work reported in this section on Nickel Contact Dermatitis above.) The past experience with metallic appliances for bone surgery was found to be 173 cases without previous experience, 17 cases with less than total joint replacement, 16 with total joint replacement and subsequent loosening and reoperations, and six with stable McKee-Farrar prostheses. Of the eleven nickel-sensitive patients, three had previous implants. Histories of nickel sensitivity showed five cases of eczema due to jewelry or garters and two cases with previous implants where the eczema appeared over the scar tissue of the site of the implant. Four individuals with positive reaction to the nickel allergen did not have a previous history of eczema. In addition, there were five patients with a history of sensitivity but not a positive reaction to the patch test.

A second phase of the study consisted of $\geq$ six postoperative patch-testing of 66 of the 198 patients without pre-operative sensitivity to patch tests. There were 55 women and 11 men, average age 69.5 years, in this group. Four of these 66 showed metal sensitivity, three to nickel and one to cobalt. This included one woman with a negative preoperative patch test but a history of eczema from garters who was positive on postoperative patch test. None of the 66, regardless of sensitivity status, had shown pain, loosening of the prosthesis, infection, or skin symptoms during the postoperative period of approximately 2 years. This represents a conversion rate of 6 percent within up to about 2 years postoperatively. A sensitivity rate of 4.6 percent to nickel by patch test was found in the 173 patients without previous bone surgery.

While nickel sensitivity in persons receiving orthopedic implants puts them at higher risk of complications, this does not represent a health problem to the population in general and is not related to exposure due to the presence of nickel in environmental media.

Chronic

In contrast to acute effects of nickel carbonyl exposure in man, little has been reported for effects of chronic exposure to this agent. Sunderman and Sunderman (1961) have described one case of chronic inhalation of nickel carbonyl at low levels, in which the patient had developed asthma and Löffler's syndrome.

Adverse pulmonary effects in man due to other nickel compounds, are noted below and discussed elsewhere in regard to occupational carcinogenicity. Russian workers (Tatarskaya, 1960; Kucharin, 1970; Sushenko and Rafikova, 1972) have observed chronic rhinitis and nasal sinusitis in workers engaged in nickel electroplating operations where chronic inahaltion of nickel aerosols such as of nickel sulfate had occurred. Associated findings commonly encountered were anosmia and nasal mucosal injury including nasal septum perforation. Asthmatic lung disease in nickel plating workers has been documented by Tolat et al. (1956) and McConnell et al. (1973). Based on various animal studies as described elsewhere, inhalation of nickel particulate matter is likely to play a role in chronic respiratory infections in nickel workers via effects on the activity of alveolar macrophages.

The role of oral nickel in dermatitic responses has also been demonstrated by Kaaber et al. (1978), who investigated the effect of a low nickel diet in patients with chronic nickel dermatitis presenting as hand eczemas of dyshidrotic morphology. Of 17 subjects in the clinical trial, nine showed significant improvement during a period of 6 weeks on a low nickel diet. Of these nine showing improvement, seven had a flare-up in their condition when placed on a normal diet. Furthermore, there was no correlation apparent between the level of urinary nickel and the degree of improvement following the diet. These authors recommend limitation in dietary nickel as a help in the management of nickel dermatitis. In this connection, also, Rudzki and Grzywa (1977) described an individual having chronic flare-ups in nickel dermatitis whose chronicity of condition was traced to the nickel content of margarine, Polish margarine having a rather high nickel content, up to 0.2 mg Ni/kg.

# IN VITRO AND IN VIVO STUDIES

## Subcellular and Cellular Aspects of Nickel Toxicity

A thorough discussion of the available information on the interactions of nickel at the molecular level is beyond the purpose of this document and consideration will be given mainly to data that are more germane to both the adverse and beneficial effects of nickel *in vivo*.

Nickel, in the form of the common divalent ion, is known to bind to a variety of biomolecular species such as nucleic acids and proteins as well as their constituent units: nucleotides, peptides, and amino acids (Natl. Acad. Sci., 1975). Of the various ligand groups for divalent nickel, strongest binding occurs to form chelate structures with sulfhydryl, aza, and amino groups, with amido-N (peptide group) and carboxyl group binding also being possible.

In the previous section dealing with nickel metabolism, it was noted that serum albumin is the main carrier protein for macromolecular-bound nickel in a number of animal species including man. It was pointed out that in man and rabbit, there also appears to be a specific nickel protein differing as to structure, such proteins possibly being evidence for an essential role for nickel.

A number of relevant reports in the literature have appeared describing *in vivo* and *in vitro* effects of various nickel compounds on enzyme systems, nucleic acid and protein synthesis as well as related effects in experimental animals. Data obtained *in vivo* are tabulated in Table 18, while *in vitro* effects are presented in Table 19.

TABLE 18. IN VIVO BIOCHEMICAL EFFECTS OF NICKEL COMPOUNDS

| Compound | Animal | Dosing conditions | Effects | Reference |
|---|---|---|---|---|
| Ni $(CO)_4$ | Rat | I.V. 20 mg/kg<br>Inhalation<br>0.20 mg/liter air | Inhibition of phenothiazine<br>Induction of benzopyrene hydroxylase in lungs and liver | Sunderman, 1967a |
| $Ni(CO)_4$ | Rat | I.V. 20 mg/kg | Inhibition of cortisone induction of hepatic tryptophan pyrrolase | Sunderman, 1967b |
| $Ni(CO)_4$ | Rat | I.V. 20 mg/kg | Inhibition of phenobarbital induction of hepatic cytochrome | Sunderman, 1968 |
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Inhibition of RNA polymerase in hepatic nuclei | Sunderman and Esfahani, 1968 |
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Incorporation of ($^{14}C$)-orotic acid into hepatic RNA | Beach and Sunderman, 1969 |
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Inhibition of RNA synthesis by hepatic chromatin - RNA polymerase complex | Beach and Sunderman, 1970 |
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Inhibition of phenobarbital induction of aminopyrene demethylase | Sunderman and Leibman, 1970 |
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Slight inhibition of leucine incorporation into liver microsomal proteins | Sunderman, 1970 |
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Elevated liver ATP level | Sunderman, 1971 |

TABLE 18. (continued)

| Compound | Animal | Dosing conditions | Effects | Reference |
|---|---|---|---|---|
| $Ni(CO)_4$ | Rat | I.V. 22 mg/kg | Inhibition of RNA synthesis in liver but not lungs | Witschi, 1972 |
| $NiCl_2$ | Rat | S.C. 16 mg/kg | Reduced liver ALA-synthetase, reduced porphyrin, cytochrome P-450, and total heme; heme oxygenase elevation in liver, kidney and cardiac tissue | Maines and Kappas, 1977 |
| $NiSO_4$ | Rat | I.P. 3 mg/kg daily, 30-90 days | At 60 to 90 days, succinic dehydrogenase reduced in liver and kidney;<br>at 30, 60 and 90 days, ATP-ase activity elevated in testes | Mathur et al., 1977 |
| Nickel (II) ion | Young mouse | | Inhibition of cytochrome oxidase, isocitric and malic dehydrogenases in liver, kidney and heart and inhibition of heart muscle phosphorylase | Weber and Reid, 1968 |
| $NiCl_2$ | Rat | I.P. 19 mg/kg, single dose<br>Oral 225 ppm long term, water | 4-fold increase in serum glucose, hyperlipidemia and insulin resistance elevated serum triglycerides | Clary and Vignati, 1973 |
| $NiCl_2$ | Rat | I.P. 250 mg/kg, single dose, 3-6 hours before sacrifice | ATP-ase activity in brain capillaries abolished Joo, 1969 | Joo, 1968 |
| $Ni_3S_2$ | Rat | I.M. | Glyceraldehyde-3-phosphate dehydrogenase inhibited; Glucose-6-phosphate dehydrogenase elevated within 6 hr. | Basrur and Swierenga, 1970 |

TABLE 19. IN VITRO BIOCHEMICAL EFFECTS OF NICKEL COMPOUNDS

| Compound | System | Exposure | Effects | Reference |
|---|---|---|---|---|
| Ni(II) ion | Rat liver microsomes | Up to 100 μM Ni | Activity of benzopyrene hydroxylase reduced to half at 0.5 μmolar Ni; total inhibition at 10 μmoles | Thompson et al., 1974 |
| Ni(II) ion | Rabbit liver and lung microsomes | Up to 50 mM Ni | N-oxidase activity enhanced 30 percent at 1 mM (liver) and 5 mM (lung), respectively. N-oxidase activity inhibited above 10 mM | Devereux and Fou 1974 |
| Ni(II) ion | DNA polymerase from avian myeloblastosis virus | Up to 8 mM Ni | Fidelity of Mg-activated DNA synthesis altered | Sirover and Loeb 1977 |
| Ni(II) ion | DNA polymerase from *E. coli* | 5 mM Ni | Fidelity of DNA synthesis altered | Miyaki et al., 1977 |
| Ni(II) ion | Rat brain synaptosomes | Up to 300 μM Ni | ATP-ase activity inhibited 20 percent at 100 μM | Prakash et al., 1973 |
| Ni(II) ion | Rat hepatic microsomes | | ATP-ase activity inhibited | Federchenko and Petrun, 1969 |
| Ni(II) ion | Cilia of *Tetrahymena pyriformis* | 5 mM Ni | ATP-ase activity inhibited | Raff and Blum, 1969 |
| Ni(II) ion | Sheep alveolar macrophages | 1 mM Ni | ATP-ase activity inhibited | Mustafa et al., 1969 |
| Ni(II) ion | Sheep alveolar macrophages | 0.5 mM Ni | ATP-creatine phosphotransferase activity inhibited | O'Sullivan and Morrison, 1963 |
| $(^{63}Ni)$ - $Ni_3S_2$ | Rat embryo muscle culture | | Inhibition of aldolase, G-6-PD, LDH, and glyceraldehyde-3-phosphate dehydrogenase | Basrur and Swierenga, 197 |

A number of investigators have studied the effects of nickel compounds on inducible enzyme systems in liver and other organs that are involved in the metabolism and detoxification of drugs and other foreign substances.

In the rat, nickel carbonyl inhibits the phenothiazine induction of benzopyrene hydroxylase in lungs and liver (Sunderman, 1967a), the cortisone induction of hepatic tryptophan pyrrolase (Sunderman, 1967b) the phenobarbital induction of hepatic cytochrome (Sunderman, 1968), and phenobarbital induction of aminopyrine demethylase (Sunderman and Leibman, 1970). Nickel carbonyl inhibition of benzopyrenehydroxylase activity probably reflects reduced enzyme biosynthesis, since *in vitro* exposure to the agent had no effect. Nickel sulfate, however, at levels greater than 1 mM does inhibit the enzyme *in vitro* (Dixon et al., 1970). Since benzopyrene is an active carcinogen, it has been suggested that a mechanism for at least co-carcinogenicity of nickel relates to increased retention of the hydrocarbon, particularly in the case of heavy cigarette smokers (Dixon et al., 1970; Sunderman, 1967a).

Maines and Kappas (1977) have reported effects of nickel (II) injection on cellular heme metabolism in rats including reduced heme levels and enhanced heme oxygenase activity. These effects could be abolished if nickel was complexed to cysteine prior to injection. In a related study, Maines and Kappas (1976) demonstrated no effect of nickel (II) ion on hepatic heme oxygenase activity *in vitro* at levels of 12.5 to 250 μM, indicating that direct activation of preformed enzyme does not occur *in vivo*.

Inhibition of RNA symthesis in the rat, probably via an effect on RNA polymerase (Sunderman and Esfahani, 1968; Beach and Sunderman, 1969, 1970; Witschi, 1972) has been demonstrated with nickel carbonyl. Moderate inhibition by this agent of hepatic protein synthesis has also been noted (Sunderman, 1970).

The inhibition of ATPase by nickel salts in vitro and in vivo has been reported for the enzyme from different sources (Prakash et al., 1973; Federchenko and Petrun, 1969; Raff and Blum, 1969; Mustafa et al., 1971; Joo, 1968 and 1969). In contrast, Mathur et al. (1977) find that ATPase activity is elevated in rat testicular tissue for all time points (30, 60, and 90 days) when rats are given Ni intraperitoneally, 3 mg/kg daily. Sunderman (1971) has suggested that the inhibition of ATPase and other ATP-requiring enzymes likely involves binding of divalent nickel to ATP, making it unavailable for subsequent utilization since it is known that nickel can form a stable complex with ATP (Sigel et al., 1967).

In vitro and in vivo studies of nickel subsulfide ($Ni_3S_2$) on muscle tissue (Basrur and Swierenga, 1970) revealed impairment of glycolytic enzyme activity.

Sirover and Loeb (1977) have demonstrated alteration of magnesium-activated DNA synthesis fidelity at 8 mM levels of nickel (II) ion and using DNA polymerase from avian myeloblastosis virus. Similar effects also are noted with E. coli DNA polymerase (Miyaki et al., 1977).

Sunderman and Sunderman (1963) found that nickel carbonyl inhalation in the rat led to increases in microsomal and supernatant fractions of lung and liver homogenates. Webb and co-workers (1972) have found that 70-90 percent of the nickel in nickel-induced rhabdomyosarcomas is found in the nucleus. Of the total nuclear nickel burden, about half is present in the nucleolus, with the remainder equally distributed between nuclear sap and chromatin. Furthermore, nickel binding to RNA and DNA was observed in nuclei of rhabdomyosarcomas from rats given nickel subsulfide intramuscularly (Heath and Webb, 1967). In mouse dermal fibroblasts grown in vitro and exposed to various $^{63}$Ni-labeled compounds, Webb and Weinzierl (1972) noted a similar distribution. These data are consistent with the findings of Beach and Sunderman (1970) that nickel is bound to the RNA polymerase-chromatin complex obtained from rat liver nuclei after nickel carbonyl exposure. Recently, Jasmin and Solymoss (1977) have reported that intrarenal administration of nickel subsulfide in the rat led to the highest relative amounts in the nuclear fraction of kidney homogenate with smaller amounts in mitochondria and microsomes.

Moffitt et al. (1972) observed that alterations in the normal subcellular distribution of nickel in rat tissue occur with the acute administration of benzopyrene (8 mg intratracheally). By 3 days postexposure, significant reductions of nickel content were seen in nucleus, mitochondria, and microsomes.

Changes in ultrastructure have been reported for various organellar components from animals exposed to nickel compounds.

In rats exposed intravenously to nickel carbonyl (65 mg/kg), ultrastructural alterations in hepatocytes included nuclear distortion by 24 hours, dilation of rough endoplasmic reticulum at 1 to 4 days, and cytoplasmic inclusion bodies at 4 to 6 days (Hackett and Sunderman, 1969).

A number of studies of the action of nickel subsulfide have included the observation of ultrastructural effects. Tumor cells from nickel subsulfide-induced rhabdomyosarcomas show pronounced alterations in ultrastructure (Basrur et al., 1970; Friedmann and Bird, 1969; Bruni and Rust, 1975) to include mitochondrial conformational changes, accumulation of electron-dense granules, and elaboration of cristae which have coalesced and formed wavy or parallel stacks in all cases. Degenerative changes, including disruption of inner and outer membranes, were sometimes seen. Some of these changes could also be detected in rat muscle tissue exposed to nickel subsulfide for relatively brief periods, 24 to 48 hours (Basrur et al., 1970). Cultured rat embryo myoblasts exposed to nickel subsulfide exhibited a variety of organellar changes (Sykes and Basrur, 1971). At the cell periphery, cytoplasmic blebs containing clusters of free ribosomes appeared to form and dissociate from the myotube while cellular organelles aggregated in the center. Alterations in the fine structure and alignment of mitochondria caused derangement of the contractile elements. Using scanning electron microscopy, Geissinger et al. (1973) showed that chromosomal abnormalities existed in a nickel subsulfide sarcoma from rat muscle tissue (20 mg intramuscularly). Neoplastic cells from renal tumors in rats induced by intrarenal administration of nickel subsulfide are characterized by large swollen mitochondria, cisternae of rough endoplasmic reticulum, abundant polysomes, lipid vacuoles, and dense bodies. Nuclei are irregular in shape with marginal chromatin and prominent nucleolus.

A number of investigators have described the effects of nickel compounds in cultures of cells. These in vitro correlates of nickel's effects in vivo have proved particularly valuable in helping elucidate the allergenic, immunological, and carcinogenic aspects of nickel toxicity in man and experimental animals.

Reports have appeared in the literature dealing with the response of alveolar macrophages and other components that serve a protective function in respiratory tract to nickel compounds. Waters et al. (1975) have studied the toxicity of nickel ion to rabbit alveolar macrophages in vitro. At a concentration of about 4 mM nickel, a 50 percent reduction in viable cells occurred, viability being determined by trypan blue exclusion. In a related study, Graham et al. (1975) studied the response of rabbit alveolar macrophages to levels of nickel that did not affect their viability. Of various metal ions tested, nickel was the only element that induced changes in phagocytic activity without significant effect on cell life. In a medium containing 1.1 mM nickel ion, these macrophages had minimal morphological evidence of injury, but lacked the ability to phagocytize polystyrene latex spheres. *In vitro* exposure of rabbit alveolar macrophages to nickel ion at 0.1 mM concentration or greater caused significant inhibition of antibody-mediated rosette formation, the extent of inhibition being concentration-dependent (Hadley et al., 1977). These results suggested to the authors that antibody-mediated rosette formation may be useful as a rapid and sensitive screen for metal toxicity.

Transformation of cultured human peripheral lymphocytes as a sensitive *in vitro* screening technique for nickel hypersensitivity versus the classical patch testing has been studied in a number of laboratories, and the earlier conflicting studies have been reviewed (Natl. Acad. Sci., 1975). The studies of Hutchinson et al. (1972), Forman and Alexander (1972), Millikan et al. (1973), Gimenez-Camarasa et al. (1975), and Svejgaard et al. (1978) have, however, established the reliability of the technique.

Jacobsen (1977) has investigated the response of cultured epithelium-like cells from human gingiva to nickel inasmuch as the element appears in dental prosthetic materials. Significant effects on cell viability are seen at nickel (II) levels down to 0.08 mM. In this study, no correlation was seen between the amount of serum present and cytotoxicity, suggesting that both complexed and uncomplexed nickel ion are equally active.

Exposure of rat embryo myoblasts in culture to nickel subsulfide dust results in drastic reduction of mitotic index and cell survival (Sykes and Basrur, 1971). Daniel et al. (1974) assessed the effect of nickel-serum complexation on cultures of chick myoblasts by pre-incubation of nickel dust in serum for up to 30 days followed by analysis of serum supernatant for nickel content. Nickel, at a level of 20 µg/l. serum and greater prevents normal cell differentiation along with cell degeneration.

Costa et al. (1978) have used various nickel compounds to assess the morphological transformations of Syrian hamster cells as a possible rapid screening technique for carcinogenicity. Using as an index the frequency of cell colony piling-up/test plate, the most pronounced effects were noted with nickel subsulfide, nickel dust, and nickel subselenide. These data are consistent with other documented comparative effects discussed below in the section dealing with nickel carcinogenicity.

Rat fat cells, when exposed to divalent nickel at levels of 1 to 6 mM, showed decreased adrenalin- and glucagon-stimulated lipolysis, along with increased glucose incorporation into lipids, possibly mimicking the action of insulin at the cell plasma membrane (Saggerson et al., 1976).

According to Taubman and Malnick (1975), nickel ion at levels of 1.0 µM-1.0 mM did not trigger histamine release from rat peritoneal mast cells, indicating that the anaphylactoid edema seen in the rat following nickel (II) injection operates by some mechanism other than a direct cellular effect.

### Synergisim and/or Antagonism

There are experimental data that demonstrate that nickel has a synergistic effect on the carcinogenicites of polycyclic aromatic hydrocarbons. Toda (1962) has found that 17 percent of rats receiving intratracheal doses of nickel oxide along with 20-methylcholanthrene developed squamous cell carcinomas; Maenza et al. (1971) demonstrated a synergistic rather than additive effect in the latency period reduction (30 percent) of sarcomas when simultaneous exposure to benzopyrene and nickel subsulfide was carried out. As stated elsewhere, the inhibitory activity of nickel on enzyme systems that mediate the metabolism of agents such as benzopyrene was noted. It is likely, then, that tissue retention of these organic compounds is prolonged with nickel exposure. Kasprzak et al. (1973) observed pathological reactions in lungs of rats given both nickel subsulfide and benzopyrene that were greater than was the case for either agent alone.

Nickel and other elements are known to be present in asbestos and may possibly be a factor in asbestos carcinogenicity. The pertinent literature has been reviewed (Morgan et al., 1973; Natl. Acad. Sci., 1975). Little in the way of experimental studies exists to shed light on any etiological role of nickel in asbestos carcinogenicity, however. Cralley (1971) has speculated that asbestos fibers may serve as a transport mechanism for metals into tissue and that the presence of chromium and manganese may enhance the carcinogenicity of nickel.

Virus-nickel synergism is suggested by the observation of Treagon and Furst (1970) that *in vitro* suppression of mouse L-cell interferon synthesis occurs in response to Newcastle Disease virus with nickel present.

### Teratogenicity

Little evidence for nickel as a teratogen has been documented. While Ferm (1972) has claimed unspecified malformations in surviving hamster embryos when mothers were exposed to parenteral nickel (0.7 to 10.0 mg/kg), Sunderman et al. (1978) found no teratogenic effects for either nickel chloride (16 mg/kg) or nickel subsulfide (80 mg/kg) in rats.

In animals, several studies have demonstrated that nickel crosses the placental barrier and is lodged in fetal tissue. Whole body analysis of offspring from rats fed nickel at dietary levels of 250 to 1000 ppm and in different chemical form showed nickel at 22 to 30 ppm in those offspring whose mothers were exposed to the highest level in diet and 12-17 ppm for the maternal exposure of 500 ppm (Phatak and Patwardhan, 1950). Lu and co-workers (1976) have reported placental transfer of nickel in pregnant mice. Intraperitoneal administration of a single dose of nickel chloride (3.5 mg/kg) at day 16 of gestation led to maximal accumulation of nickel in fetal tissue at 8 hours post-exposure, while peak levels of nickel in maternal blood and placentae were observed 2 hours afterwards. In a recent detailed study by Sunderman et al. (1978), the uptake of $^{63}$Ni label given intramuscularly to rats was seen in embryo and embryonic membrane at day 8 of gestation, the amount of label being equivalent to that in maternal lungs, adrenals and ovaries. Furthermore, autoradiograms revealed nickel label in yolk sacs of placentae 1 day post injection (day 18 of gestation) and some passage of label into fetal tissue. On day 19, fetal urinary bladder had the highest level of label.

The data of Phatak and Patwardhan (1950) on litter sizes from pregnant rats fed nickel in various forms at a level of 1000 ppm suggest a reduction in pup numbers at this exposure level. Schroeder and Mitchener (1971) followed three generations of rats continuously exposed to nickel in drinking water (5 ppm). Increased numbers of runts and enhanced neonatal mortality were seen in each of three generations, along with a significant reduction in litter size and a reduced proportion of males in the third generation. In a similar endeavor, Ambrose et al. (1976) followed three generations of rats given nickel in diet at concentrations of 250 to 1000. There was increased fetal mortality in the first generation while body weights were decreased in all generations at 1000 ppm. Ferm (1972) noted that intravenous administration of nickel acetate (0.7-10.0 mg/kg) to pregnant hamsters at day 8 of gestation resulted in increases in the number of resorbed embryos.

## Gametotoxic Effects of Nickel

When nickel sulfate was administered to rats subcutaneously at a dosing of 2.4 mg Ni/kg, Hoey (1966) observed shrinkage of central tubules, hyperemia of intertubular capillaries and disintegration of spermatozoa in testicular tissue 18 hours after a single dose. Multiple dosing produced disintegration of spermatocytes and spermatids and destruction of Sertoli cells. Such effects were noted to be reversible. Von Veltschewa et al. (1972) noted inhibition of spermatogenesis in rats given daily oral doses of nickel suflate (25 mg/kg) with reduction in the number of basal cells within the tubules and in the number of spermatozoa-containing tubules. Continuation of the dosing regimen for 120 days resulted in complete obliteration of fertility in these animals.

No gametotoxic effects have been documented in man.

## Carcinogenicity

The present status of nickel's role in occupational and experimental carcinogenesis has been the subject of a number of reviews (Int. Agency Res. Cancer, 1976; Natl. Acad. Sci., 1975; Natl. Inst. Occup. Safety Health, 1977; Sunderman, 1973, 1976, 1977).

A carcinogenic response to various nickel compounds upon injection has been observed in a number of animal studies (Sunderman et al., 1975, 1976; Lau et al., 1972; Stoner et al., 1976; IARC. 1976). In nickel refinery workers, an excess risk of nasal and lung cancers has been demonstrated (IARC, 1976). However, there is no evidence at present that orally ingested nickel is tumorigenic.

## Experimental Carcinogenesis

The qualitative and quantitative character of the carcinogenic effects of nickel as seen in experimental animal models has been shown to vary with the chemical form of the nickel, the routes of exposure, the animal model employed (including strain differences within animal models), and the amounts of the substance employed.

Some of the experimental models of nickel carcinogenesis which have evolved out of various laboratories are given in Table 20, along with the various carcinogenic nickel compounds employed, the levels of material used and the routes of administration. Responses are usually at the site of injection, although in the case of nickel acetate injection, pulmonary carcinomas were detected in mice given repeated intraperitoneal injections (Stoner et al., 1976). There have been no reports of experimental carcinogenesis induced by oral or cutaneous exposure.

Nickel metal, in the form of dust or pellets, leads to induction of malignant sarcomas at the site of dosing in rates, guinea pigs, and rabbits (Hueper, 1955; Heath and Daniel, 1964; Heath and Webb, 1967; Mitchell et al., 1960), while inhalation of nickel dust leads to lung anaplastic carcinomas and adenocarcinomas (Hueper, 1958).

In a study of the carcinogenicities of various metal compounds, Gilman (1962) noted that nickel subsulfide ($Ni_3S_2$) was a potent inducer of rhabdomyoscarcomas when given intramuscularly. Later studies of the carcinogenicity of nickel subsulfide demonstrated adenocarcinomas in rats given the substance intrarenally (Jasmin and Riopelle, 1976), rhabdomyosarcomas, fibrosarcomas, and fibrohistocytomas in rat testicular tissue after intratesticular dosing (Damjanov et al., 1978) and lung epidermoid and adenocarcinomas in rats inhaling nickel subsulfide (Ottolenghi et al., 1974).

TABLE 20. EXPERIMENTAL MODELS OF NICKEL CARCINOGENESIS

| Animal | Agent | Dosing | Response | Reference |
|---|---|---|---|---|
| Rat, mice | Ni dust | Intrapleural/intraosseous: 0.06% suspension 5% suspension | Sarcomas | Hueper, 1955 |
| Guinea pig | Ni dust | Inhalation 15 mg 1 $m^3$ | Lung anaplastic carcinomas and adenocarcinomas | Hueper, 1958 |
| Rat | Ni dust | I.M., 28 mg in serum | Rhabdomyosarcomas | Heath and Daniel 1967; Heath an Webb, 1967 |
| Rat | Ni dust | I/P., intrathoracic 5 mg in saline | Mesotheliomas | Furst et al., 19 |
| Rat | Ni pellet | S.C., 2 x 2 mm | Sarcomas | Mitchell et al., 1960 |
| Rat, mouse | $Ni_3S_2$ or NiO dust | I.M., 20 mg/thigh | Rhabdomyosarcomas | Gilman, 1962 |
| Syrian hamster | $Ni_3S_2$ | I.M., 5 or 10 mg, single | Sarcomas | Sunderman et al. 1977 |
| Rat | $Ni_3S_2$ | Inhalation ca 1 mg/$m^3$ | Epidermoid carcinomas and adenocarcinomas (lung) | Ottolenghi et al 1974 |
| Rat | $Ni_3S_2$ | Intrarenal 5 mg/saline or glycerol | Renal adenocarcinomas | Jasmin and Riope 1976 |
| Rat | $Ni_3S_2$ | Intratesticular, 0.6-10 mg | Fibrosarcomas and rhabdomyosarcomas | Damjanov et al., 1978 |

TABLE 20 (continued)

| Animal | Agent | Dosing | Response | Reference |
|---|---|---|---|---|
| Rat | $Ni(CO)_4$ | Inhalation, 4-80 ppm | Epidermoid and anaplastic carcinoma, and adenocarcinomas (lung) | Sunderman et al., 1959; Sunderman and Donnelly, 1965 |
| Rat | $Ni(CO)_4$ | I.V., 50 µl/kg | Carcinomas and sarcomas | Lau et al., 1972 |
| Mouse | $Ni(Oac)_2$ | I.P., 360 mg/kg | Lung adenocarcinomas | Stoner et al., 1976 |
| Rat, hamster | Nickelocene | I.M. | Sarcomas | Haro et al., 1968<br>Furst and Schlauder, 1971 |
| Rat | $Ni^3S^2$/ Benzpyrene | I.M., 10 mg/5 mg | Sarcomas | Maenza et al., 19 |
| Rat | $Ni^3S^2$/ Benzpyrene | Intratracheal: 2-5 mg | Squamous cell carcinomas | Karsprzak et al., 1968 |
| Rat | NiO/ methylcholanthrene | Intratracheal: | Squamous cell carconimas | Toda, 1962 |

Exposure to nickel carbonyl either via inhalation (Sunderman et al., 1959; Sunderman and Donnelly, 1965) or intravenously (Lau et al., 1972) has been observed to induce pulmonary carcinomas or carcinomas and sarcomas in organs such as liver and kidney, respectively. As noted above, repeated dosing intraperitoneally yields lung carcinomas in mice (Stoner et al., 1976) when nickel acetate is used, while nickelocene, an organonickel "sandwich" structure, induces sarcomas in rats and hamsters when given intramuscularly (Haro et al., 1968; Furst and Schlauder, 1971).

The underlying biochemical mechanisms governing the carcinogenicities of various nickel compounds have yet to be fully elucidated.

Transport to the site(s) of carcinogenic action is known to differ among carcinogenic nickel agents. As noted earlier, nickel carbonyl decomposes extracellularly, and the liberated nickel is oxidized intracellularly and mobilized. In the case of insoluble dusts, such as metallic nickel and nickel subsulfide, slow dissolution from extracellular deposition by extracellular fluid presumably occurs.

Nickel dust gradually dissolves when incubated with horse serum to yield complexes of oxidized nickel with proteins and amino acids (Weinzierl and Webb, 1972) while ultrafiltrable nickel complexes obtained by adding nickel dust to muscle homogenate _in vitro_ are similar to those formed when nickel implants slowly dissolved in muscle (Weinzierl and Webb, 1972). Webb and Weinzierl (1972) using $^{63}$Ni label have demonstrated that mouse dermal fibroblasts in culture take up nickel complexes with proteins and other ligands, and they suggest that myoblasts involved in repair of muscle injured by dust contact take up solubilized nickel and undergo subsequent neoplastic transformation.

Singh and Gilman (1973), in a study using double-diffusion chambers containing nickel subsulfide implanted intraperitoneally in rats, observed effects on rhabdomyocytes 2 to 24 days later, indicating the intermediacy of a soluble nickel complex, since the technique interposes a solution barrier between agent and cellular surface. Using $^{63}$Ni-labeled nickel subsulfide, Sunderman et al. (1976), observed that intramuscular administration in rats was followed by localization within macrophages and fibroblasts by the end of the first week. In a related report, Kasprzak and Sunderman (1977) monitored the relative rates of dissolution of labeled nickel ($^{63}$Ni) subsulfide in water, whole rat serum, and rat serum ultrafiltrate. Dissolution rates were more rapid in serum or serum ultrafiltrate and were attended by formation of nickel sulfide and nickel hydroxide. These authors speculate that subsequent solubilizing of these latter forms _in vivo_ is conceivable owing to the lower pH existing in lysosomes, nickel particles being observed in the lysosomes of macrophages from nickel subsulfide-treated rats (Sunderman et al., 1976).

Experimental clues as to the ways in which intracellular nickel imparts neoplastic formation include the following: (1) The intracellular distribution of nickel in nickel-induced rhabdomyosarcomas is highest in the nucleus (70-90 percent), with roughly half of this amount being in the nucleolus. (2) Nickel is bound to an RNA polymerase-chromatin complex from hepatic cell nuclei of rats with nickel carbonyl; (3) this complex carries out diminished RNA synthesis; (4) the fidelity of DNA synthesis is impaired in various cell types _in vitro_; (5) addition of nickel ion to cultures of mouse L-929 cells interferes with interferon synthesis (Treagon and Furst, 1970); and (6) addition of nickel subsulfide to cultured embryonic muscle cells inhibits mitotic activity and causes abnormal mitotic figures (Basrur and Gilman, 1967; Swierenga and Basrur, 1968).

The above discussion has focused on nickel compounds used alone to induce carcinogenic responses. An equally important aspect of these effects is the synergistic action of nickel in the carcinogenicity of other agents, since environmental situations entail simultaneous exposure to a number of such substances. Discussion of this area has been presented previously under the Synergism and/or Antagonism section.

Comparative carcinogenicity for various nickel compounds has been studied and demonstrated in various laboratories (Sunderman and Maenza, 1976; Jasmin and Riopelle, 1976; Gilman, 1962; Payne, 1964). Furthermore, there is a general inverse relationship between solubility and carcinogenic potential: insoluble nickel metal, nickel oxide, and nickel subsulfide are carcinogenic, while most of the nickel salts are noncarcinogens. A few exceptions to this do exist: nickel acetate, for example, is soluble but also has carcinogenic character (Table 20). This relationship reflects mainly the relative speed of clearance of soluble nickel from the organism by the renal excretion, the time for clearance being shorter than the induction interval for carcinogenic manifestations.

Sunderman and Maenza (1976) studied the incidence of sarcomas in Fischer rats within 2 years after single intramuscular injections of four insoluble nickel-containing powders: metallic nickel, nickel sulfide, α-nickel subsulfide and nickel-iron sulfide matte. Amorphous nickel sulfide had no tumorigenic potential, while nickel subsulfide was most active. The relative carcinogenicity of nickel-iron sulfide matte was intermediate between nickel subsulfide and metallic nickel powder, suggesting to these authors that there may also be a previously unrecognized carcinogenic potential in other nickel-sulfur mineral complexes, as well as the corresponding arsenides, selenides, and tellurides.

## Epidemiology

The epidemiological data on the carcinogenicity of nickel is reported for occupationally exposed nickel refinery workers from a number of countries. Cancer of the respiratory tract, specifically the lung and nasal cavities, among nickel refinery workers has been cited in these reports. The variety of processes for different raw nickel materials results in the production of different nickel compounds and consequently, workers at specific refineries at different work stations are exposed in significantly different ways.

The data have been summarized and reviewed by numerous authors and, since the evidence is incontrovertible, there has been universal agreement that nickel refinery workers are at significantly higher risk for cancer of the lungs and nasal cavity (Natl. Acad. Sci., 1975; Int. Agency Res. Cancer, 1976; Natl. Inst. Occup. Safety Health, 1977; Sunderman, 1977). Sunderman (1977), in a review, points out that in addition to the significantly high risk for cancer of the lungs and nasal cavities, increased risk has been found for cancer of the larynx in Norwegian refinery workers and for gastric cancer and soft tissue sarcoma in Russian refinery workers.

According to the IARC (1976): "Epidemiological studies conclusively demonstrate an excessive risk of cancer of the nasal cavity and lung in workers at nickel refineries. It is likely that nickel in some form(s) is carcinogenic to man."

Summaries of the cancer risks demonstrated in epidemiological and occupational studies are given in Tables 21 and 22, respectively.

The nickel compounds which are implicated are insoluble dusts of nickel subsulfide ($Ni_3S_2$) and nickel oxides ($NiO$ and $Ni_2O_3$) the vapor of nickel

TABLE 21. EPIDEMIOLOGICAL STUDIES OF NICKEL CARCINOGENESIS

| Agent | Dosing | Response | Organ/Tissue | Industry | Reference |
|---|---|---|---|---|---|
| Nickel Matte Concentrated Feed stock | Inhalation | Carcinoma | Lung Nasal | Clydach, Wales refinery workers | Doll, 1977 |
| Nickel dust and fumes | Inhalation | Carcinoma epidermoid anaplastic adena | Lung | Falconbridge refinery-Norway | Kreyberg, 1978 |
| Unknown | Inhalation | Precancerous lesions | Biopsies of mucosa from middle turbinate | Falconbridge refinery-Norway | Torjussen and Solberg, 1976 |
| Ni oxides, Ni Alloys, Ni sulfate and Ni chloride | Inhalation >0.3 mg $Ni/m^3$ | Cancer | Lung | Aircraft engine factory | Bernacki, 1978 |

TABLE 22. OCCUPATIONAL STUDIES OF NICKEL CARCINOGENESIS

| Agent | Dosing | Response | Organ/Tissue | Industry | Reference |
|---|---|---|---|---|---|
| Insoluble dusts | | | | | |
| $Ni_3S_2$ | Inhalation | Carcinoma | Lung Nasal | Refinery | Sunderman, 1973 |
| NiO; $Ni_2O_3$ | | epidemoid | 69% 45% | | |
| | | anaplastic | 27% 12% | | |
| | | pleomorphic | 0 31% | | |
| Vapors | | | | | |
| $Ni(CO)_4$ | | | | | |
| Soluble aerosols | | | | | |
| $NiSO_4$ | | | | | |
| Ni(NO$_3$)2 or Ni $Cl_2$ | Inhalation | | Kidney | Canadian refinery electrolytic workers | Sunderman, 1977 |
| Ni dusts | Inhalation | Cancer | Lung Nasal<br>Larynx | Norwegian refinery | Pedersen, et al. 1973 |
| Soluble and insoluble Ni compounds plus arsenic and cobalt dusts | Inhalation | Carcinomas<br>Sarcoma | Gastric<br>Soft tissue | Russian refinery | Saknyn and Shabynina, 1973 |

carbonyl [$Ni(CO)_4$]; and soluble aerosols of nickel sulfate, nitrate, or chloride ($NiSO_4$, $NiNO_3$, $NiCl_2$) (Sunderman, 1977).

Inasmuch as respiratory tract cancers have occurred in industrial facilities that are metallurgically diverse in their operations, carcinogenicity probably resides in several compounds of nickel (Natl. Acad. Sci., 1975). This is certainly consistent with the animal models of carcinogenicity previously described. Furnace workers appear to have the highest risk in this regard, and freshly formed hot nickel dusts from some roasting procedures may be especially carcinogenic.

In Table 23 is an earlier tabulation (Natl. Acad. Sci., 1975) of the numbers of different types of cancers of the lung and nasal cavities seen in nickel workers. As of March 1977, Sunderman (1977) had tabulated 477 cases of lung cancer and 143 cases of cancers of the nose and perinasal sinuses. Other excess cancer risk categories reported are laryngeal cancers in Norwegian nickel refinery workers (Pedersen et al., 1973), gastric and soft tissue carcinomas in Russian nickel refinery employees (Saknyn and Shabynina, 1973), and the relatively rare renal cancer in Canadian nickel electrolytic refinery workers (Sunderman, 1977).

The earliest epidemiological investigation of the increased risk of cancer is that of the nickel refinery workers at Clydach, Wales, where the Mond refining process had been used since the opening of the refinery in 1900. The mortality experience of these workers has been monitored continuously. The systematic retrospective investigations showed that there were significant changes in risk for workers beginning employment after 1925, since the refinery had undergone basic changes which resulted in control of pollutants and decrease of exposure by that time.

## TABLE 23. HISTOPATHOLOGICAL CLASSIFICATION OF CANCER OF THE LUNG AND NASAL CAVITIES IN NICKEL WORKERS[a]

| Tumor Classification | Lung Cancer | | Nasal-Cavity Cancer | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Epidermoid carcinoma (squamous cell) | 34 | 69 | 22 | 45 |
| Anaplastic (undifferentiated) carcinoma | 13 | 27 | 6 | 12 |
| Alveolar cell carcinoma | 1 | 2 | 0 | 0 |
| Adenocarcinoma | 1 | 2 | 0 | 0 |
| Columnar cell carcinoma | 0 | 0 | 2 | 4 |
| Spheroidal cell carcinoma | 0 | 0 | 1 | 2 |
| Spindle cell carcinoma | 0 | 0 | 1 | 2 |
| Scirrhus carcinoma | 0 | 0 | 1 | 2 |
| Pleomorphic carcinoma | 0 | 0 | 15 | 31 |
| Reticulum cell carcinoma | 0 | 0 | 1 | 2 |
| TOTALS | 49 | 100 | 49 | 100 |

[a] From Natl. Acad. Sci., 1975.

Doll et al. (1977) reports on an update of the mortality experience of the Clydach workers, extending the number of men and the years at risk back in time for inclusion and extending the observation time for mortality forward. Tables 24, 25, and 26 show the data for Clydach which led Doll and his associates to revise the time of the reduction of the risk of cancers from "by 1925" to "until 1930."

The epidemiological studies of cancer of the respiratory tract in nickel refinery workers had not considered the role of smoking. Kreyberg (1978) reports on a study of the nickel refinery workers from the Falconbridge refinery near Kristiansand, Norway. The previous epidemiological studies of this worker population had established their higher risk for cancer of the lungs and determined that this elevated risk was limited to workers involved in the roasting, smelting, and electrolysis processes. This earlier work did not differentiate the lung cancers histologically, nor did it take account of smoking behavior. Kreyberg and associates were able to re-examine the data for the Falconbridge refinery workers and determine histological characteristics of lung cancers, the age at start of employment of the cases, their lifetime smoking history employment history at Falconbridge and age at diagnosis. The total number of cases examined was 44.

The total number of workers over Falconbridge's history from 1927 until 1975 was available. Figure 10 shows the number of workers over this time, those exposed and not exposed, both in permanent and temporary positions, and the number and types of lung cancers by years of diagnosis. The gap of cases between 1950 and 1958 became the focus of the study. Employment records led to the separation of the 44 cases into two series. Series I includes 18 cases who started employment between 1927 and 1939 (members of a cohort observed for

TABLE 24. NUMBER OF MEN FIRST EMPLOYED AT CLYDACH NICKEL REFINERY, WALES[a] AT DIFFERENT PERIODS AND MORTALITY OBSERVED AND EXPECTED FROM ALL CAUSES[a]

| Year of first employment | No. of men | Man-years of risk | Number of deaths Observed | Number of deaths Expected | Ratio of observed and expected deaths O/E |
|---|---|---|---|---|---|
| Before 1910 | 119 | 1,980.0 | 117 | 102.01 | 1.15 |
| 1910-14 | 150 | 2,2666.5 | 137 | 92.84 | 1.48 |
| 1915-19 | 105 | 2,204.0 | 89 | 55.44 | 1.61 |
| 1920-24 | 285 | 7,126.5 | 209 | 146.25 | 1.43 |
| 1925-29 | 103 | 2,678.0 | 60 | 51.91 | 1.16 |
| 1930-44 | 205 | 4,538.5 | 77 | 60.42 | 1.27 |
| All periods | 967 | 21,193.5 | 689 | 508.87 | 1.35 |

[a] From Doll et al. (1977).

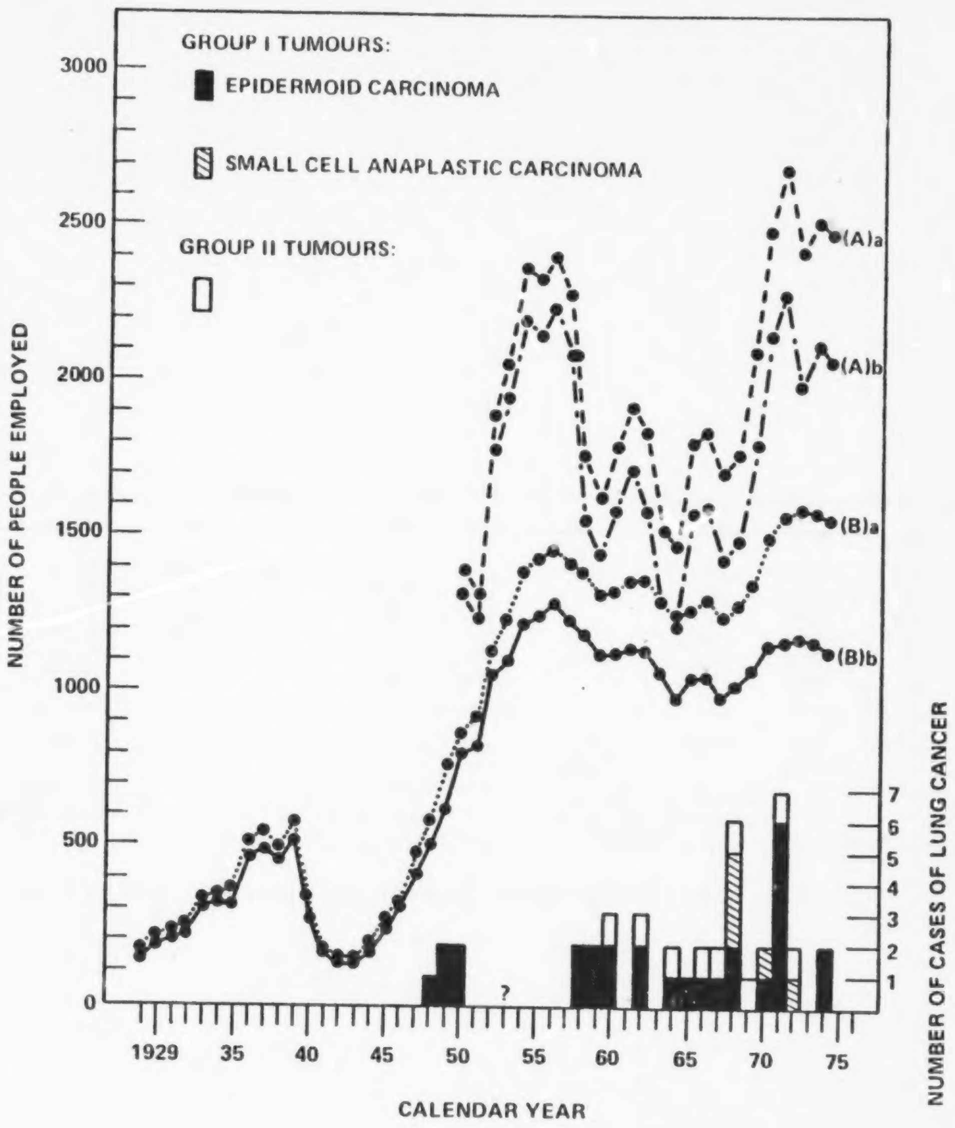

Figure 10. Lung cancer cases diagnosed 1929-1975 at Falconbridge. Plots of number of people employed at Falconbridge nickel refinery (curves) and number of new cases of lung cancer diagnosed between 1929 and 1975 (histogram): (A) number of people on the payroll (a = total number, b = those occupationally exposed to nickel); (B) number of people in established positions (a = total number, b = those occupationally exposed to nickel). The two cases from 1951 with development time of 1 year or less are not included. From Kreyberg (1978).

TABLE 25. MORTALITY BY CAUSE AND YEAR OF FIRST EMPLOYMENT, CLYDACH NICKEL REFINERY, WALES[a]

| Year of first employment | No. deaths from nasal sinus cancer[b] | | | No. deaths from lung cancer | | | No. deaths from other malignant neoplasms | | | No. deaths from other diseases | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Observed | Expected | Ratio O/E | Observed | Expected | O/E | Ratio Observed | Expected | Ratio O/E | Observed | Expected | Ratio O/E |
| Before 1910 | 14 | 0.036 | 389 | 24 | 2.389 | 10.0 | 10 | 14.637 | 0.68 | 69 | 84.95 | 0.81 |
| 1910-14 | 24 | 0.137 | 649 | 34 | 3.267 | 10.4 | 10 | 13.549 | 0.74 | 69 | 75.99 | 0.91 |
| 1915-19 | 11 | 0.025 | 440 | 20 | 3.070 | 6.5 | 10 | 8.064 | 1.24 | 48 | 44.28 | 1.08 |
| 1920-24 | 7 | 0.071 | 99 | 50 | 9.642 | 5.2 | 27 | 20.902 | 1.29 | 125 | 115.63 | 1.08 |
| 1925-29 | 0 (1) | 0.026 | 0 | 9 | 3.615 | 2.5 | 7 | 7.247 | 0.97 | 44 | 41.02 | 1.07 |
| All periods before 1930 | 56 (2) | 0.195 | 287 | 137 | 21.983 | 6.2 | 64 | 64.399 | 0.99 | 355 | 361.87 | 0.98 |
| 1930-44 | 0 | 0.034 | 0 | 8 | 5.463 | 1.5 | 11 | 8.786 | 1.25 | 58 | 46.14 | 1.25 |

[a] From Doll et al. (1977).

TABLE 26. CHRONOLOGICAL CHANGES IN THE FEED MATERIAL AT CLYDACH NICKEL REFINERY, WALES[a]

| | Composition of nickel mate | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Period | Ni, percent | Cu, percent | S, percent | Fe, percent | As, ppm | Se, ppm | Te, ppm | Pb, ppm |
| 1902-33 | 40-45 | 35-40 | 16 | 1 | 0.3 | trace | trace | trace |
| 1933-64 | 75 | 2-6 | 23 reducing to 0.7 | 1 | 0.3 | trace | trace | trace |
| 1964-76 | 75 | 2-5 | 0.3 | 0.7 | 0.3-0.1 | 50 | 80 | 0.2-0.4 |

[a] From Doll et al. (1977).

35 to 47 years, and almost complete mortality data) with a mean age of 28.6 years at start of employment and a range of 19 to 38 years. Series II comprises 26 cases who started employment in 1946 (from a cohort observed for at most 30 years) with a mean age at start of employment of 38.3 years and a range of 24 to 55 years.

Tumors were identified as Group I (epidermoid and small cell anaplastic carcinoma) and Group II (adenocarcinomas and others). Figure 11 shows the development time for the two tumor groups for the cases in the two series. The sharp differences for the developmental time for the two series are striking. The relationship of the time of development, year of start of employment and year of diagnosis is shown in Figure 12.

The age at diagnosis for Group I tumor cases in Series I and II is shown in Table 27. This table also shows the data for a control group of cases from the Norwegian general population. There is remarkable agreement between Series I, II and the controls for mean age at diagnosis.

The Norwegian experience has shown an increase in the ratio of Group I/II tumors since 1948-50. Group I tumors are associated with cigarette smoking, and the proportionate increase of Group I cases is generally attributed to increase in cigarette smoking. The smoking status of the cases is shown in Table 28.

The 32 Group I cases had only three possible nonsmokers, but four of seven Group II cases were documented nonsmokers. The number of cases, seven, for Group II is small, but the nonsmoking/smoking ratio of 4/3 in the counties from which the Falconbridge workers are drawn is not unusual. The implication is strong that tobacco carcinogens play a significant role in the development of Group I cases, as well as the exposure to nickel. Most of the workers

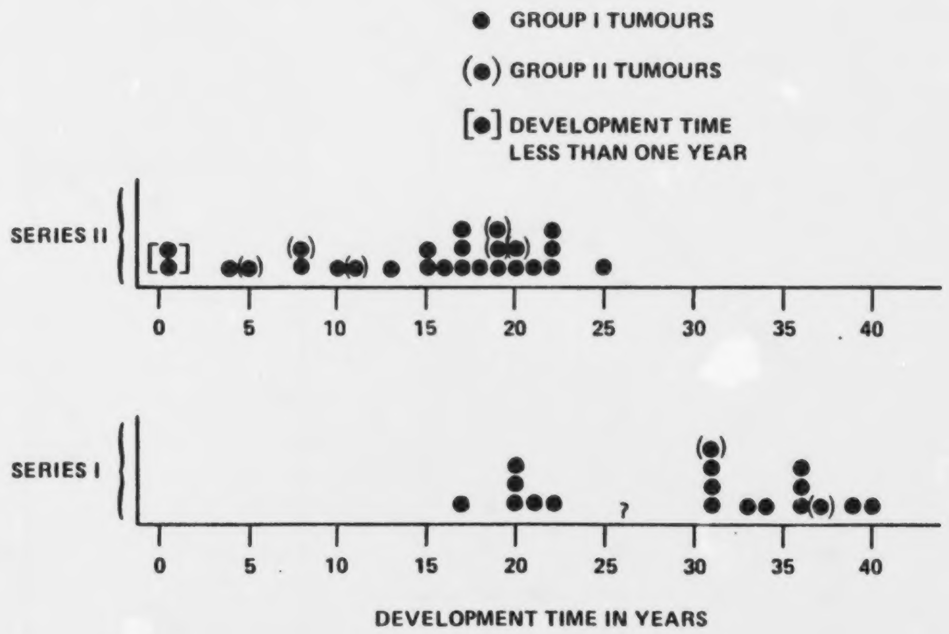

Figure 11. Development time for lung tumours in Series I and Series II workers in a nickel refinery. From Kreyberg (1978).

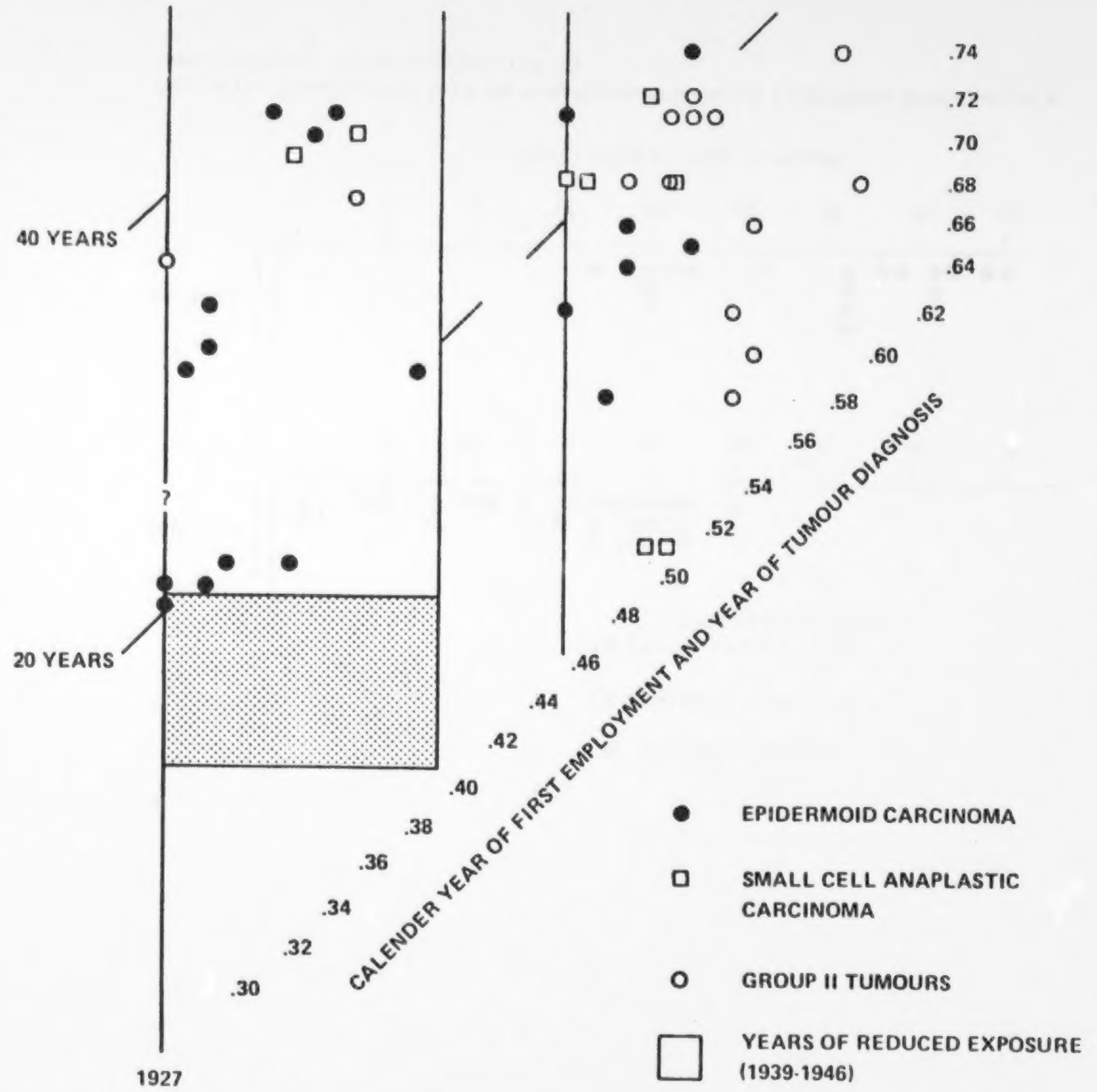

Figure 12. The scatter of occurrence of lung tumors related to time of first employment (abscissa) and time of diagnosis of tumor(ordinate). From Kreyberg (1978).

## TABLE 27. AGE AT TIME OF DIAGNOSIS OF GROUP I TUMORS OF WORKERS EXPOSED TO NICKELa

| Series | No. of cases | Age, years |  |  |
|---|---|---|---|---|
|  |  | Mean | Minimum | Maximum |
| I | 15 | 57.6 | 40 | 75 |
| II | 17 | 56.0 | 44 | 73 |
| Kreyberg (1969) | 596 | 58.2 | 31 | 75+ |

[a] From Kreyberg (1978).

## TABLE 28. SMOKING AND TUMOR INCIDENCE IN WORKERS AT THE FALCONBRIDGE NICKEL REFINERY[a]

| Type of tumor | Smokers | Nonsmokers |
|---|---|---|
| Series I |  |  |
| Epidermoid carcinoma | 10 | 3 (?)[b] |
| Small cell anaplastic carcinoma | 2 | 0 |
| Group II tumor | 0 | 2 |
| Series II |  |  |
| Epidermoid carcinoma | 13 | 0 |
| Small cell anaplastic carcinoma | 4 | 0 |
| Adenocarcinoma | 3 | 2 |

[a] From Kreyberg (1978).

[b] Smoking history not ascertainable. Allocation as nonsmokers is the assumption against the hypothetical relationship.

started smoking years before being exposed to nickel; thus the nickel exposure can be relegated, at least temporally, to a secondary role.

The development time of cancer when defined as the interval between the start of exposure to nickel and time of diagnosis has been confusing and not useful as a variable. However, when development time to tobacco use is used, the picture clarifies. In Norway, the starting age for cigarette smoking is between 13 and 18 years, and the mean age at diagnosis can be explained. The authors conclude that the developmental time due to nickel alone is obscured and is unknown at present, The presence of more than one carcinogen makes it difficult if not impossible to determine developmental time. "The incidence may be increased when weak carcinogens are involved without the mean age at diagnosis being markedly altered" (Kreyberg, 1978).

The medical department of the Falconbridge refinery monitors exposed workers by obtaining urine and plasma nickel concentrations, enforces safety precautions such as wearing respirators, protective clothing, showering, and discourages smoking. In respect to prevention of cancers of the nasal cavity, the workers at risk are asked to rinse out their noses with the aid of a syringe and are examined periodically for pathology of the nose and sinuses.

Torjussen and Solberg (1976) report on a study of 92 randomly selected workers from Falconbridge exposed to nickel compounds and 37 nonexposed workers as control. Biopsies of mucosa from the middle turbinate were examined for precancerous lesions. All workers were without known nasal disease. All biopsy samples showed inflammatory changes, with more in the exposed than nonexposed group. The exposed group showed 17 percent atypical epithelial changes, while no such changes were found in the control group. These changes were not related to age and smoking habits. These lesions were considered precancerous.

The cancer risk status in workers exposed to nickel in workplaces other than nickel refineries is not established at this time. Since the nickel compounds associated with the refining processes may also occur in other industries, investigations clearly should be conducted.

Bernacki et al. (1978) reports on a pilot study of exposure to nickel and lung cancer mortality in an aircraft engine factory. The investigators did not find an increased relative risk for workers exposed to nickel compounds. The atmospheric concentrations were low, below 1 mg Ni/m$^3$, the Occupational Safety and Health Administration threshold limit value, and the nickel compounds were not identified.

While nickel is found in asbestos fibers in varying amounts, the etiological role of nickel as a co-carcinogen in the presence of asbestos has not prompted any epidemiological studies of this association.

## CRITERION FORMULATION

### Existing Guidelines and Standards

The threshold limit values (TLV) for a work day exposure has been set at 1 ppb (Am. Conf. Gov. Ind. Hyg. 1971).

### Current Levels of Exposure

The route by which most people in the general population receive the largest portion of daily nickel intake is through food. Based on the available data from composite diet analysis, between 300 to 600 µg nickel per day are ingested. Fecal nickel analysis, a more accurate measure of dietary nickel intake, suggests about 300 µg/day. The highest level of nickel observed in water was 75 µg per liter. Average drinking water levels are about 5 µg/l. A typical consumption of 2 liters daily would yield an additional 10 µg of nickel, or which up to 1 µg would be absorbed.

### Special Groups at Risk

Occupational groups such as nickel workers and other workers handling nickel comprise the individuals at the highest risk. Women, particularly housewives, are at special risk to nickel-induced skin disorders. Approximately 47 million individuals, comprising the smoking population of the United States, are potentially at risk for possible co-factor effects of nickel in adverse effects on the respiratory tract.

### Basis for Derivation of Criterion

In arriving at a standard for nickel, several factors must be taken into account. There is little evidence for accumulation of nickel in various tissues. Absorption through the gastrointestinal tract is minimal. Acute exposure of man to nickel is chiefly of concern in workplaces where nickel carbonyl or nickel dust are present at high levels. In these situations, inhalation is the main route of entry and the lung is the critical organ although, in some instances of high exposure, the central nervous system may also be involved.

The major problem posed by nickel for the U.S. population at large is nickel hypersensitivity, mainly via contact with many nickel-containing commodities. Nickel could play a role in altering defense mechanisms against xenobiotic agents in the respiratory tract, leading to enhanced risk for respiratory tract infections.

While nickel has a possible role as a co-carcinogen in producing respiratory cancer, as suggested by animal studies, this remains to be demonstrated. There is no evidence for carcinogenicity due to the presence of nickel in water. The role of nickel as an essential element is a confounding factor in any risk estimate.

In order to develop a risk assessment based on toxicological effects other than carcinogenicity, dose-response data would be most helpful. However, while the frequency or extent of various effects of nickel are related to the level or frequency of nickel exposure in man, the relevant data do not permit any quantitative estimation for dose-response relationships. The lowest levels of nickel associated with adverse health effects, therefore, must be used in establishing a criterion level for nickel in drinking water.

To arrive at a risk estimate for nickel, a modification of the approach used for non-stochastic effects (Fed. Register 44(52):15980, March 15, 1979) has been adopted.

The studies cited in this document have not demonstrated a no-observable-effect level (NOEL). Therefore, the study demonstrating the lowest-observable-effect level (LOEL) for nickel in drinking water has been used to arrive at a non-stochastic risk estimate.

In the study of Schroder and Mitchner (1971), adverse effects in rats were demonstrated at a level of 5 mg/l (5 ppm) in drinking water. Three generations of rats were continuously exposed to 5 mg/l (5 ppm) of nickel in drinking water. In each of the generations, increased numbers of runts and enhanced neonatal mortality were seen. A significant reduction in litter size and a reduced proportion of males in the third generation also were observed.

To adapt the LOEL into an Acceptable Daily Intake (ADI) for man, the LOEL is divided by an uncertainty factor of 100, as detailed in a recent National Academy of Science report (Drinking Water and Health, pp. 803-04, NAS, 1977) and adopted by The U.S. Environmental Protection Agency (Fed. Register 44(52):15980, March 15, 1979). The choice of this factor is based on the absence of long-term or acute human data, scanty results on experimental animals, and an absence of evidence for carcinogenicity.

If the 5.0 mg/l level were used in the standard water quality criteria, the criterion can be determined to be 133 µg/l.

$$\frac{5(\text{mg/l}) \times 25 \text{ ml/day/rat}}{.3(\text{kg/av. rat})} = \frac{125}{.3}$$

$$= 416.67\ \mu g$$

$$\simeq 420$$

dose/day/av. rat

$$\frac{420}{100} = 4.2\ \mu g \text{ (ADI)}$$

$$4.2 \times 70 = 294\ \mu g \text{ (ADI for 70 kg/man)}$$

$$2(X) = (\text{Av. Fish intake})(\text{BCF})(X) = \text{Daily Intake}$$

$$2(X) + (0.0187)(11)(X) = 294\ \mu g$$

$$2.205\ X = 294\ \mu g$$

$$X = 133\ \mu g/l \text{ (criterion)}$$

2 = amount of water ingested, liters/day

X = Ni concentration, mg/l

0.0187 = amount of fish/shellfish products consumed, kg/day

$F = 11 \text{ (BCF)}, \frac{\text{mg Ni/kg fish}}{\text{mg Ni/l of water}}$

Drinking water contributes 91 percent of the assumed exposure while eating contaminated fish products accounts for nine percent. The criterion level for nickel can alternatively be expressed as 1.4 mg/l, if exposure is assumed to be from the consumption of fish and shellfish products alone.

$$X \times 0.0187 \times 11 = 294\ (\mu g/l)$$

$$X \times 0.2057 = 294$$

$$X = 1.429 \text{ mg}$$

$$X = 1.4 \text{ (mg/l)}$$

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